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DENTAL DEVELOPMENT IN CONGENITAL SYPHILIS

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A critical analysis of the dental manifestations in congenital syphilis is timely in view of the recent educational, experimental and clinical efforts to reduce the incidence of this disease. The purpose of this investigation was to determine the characteristic clinical, roentgenographic and histologic dental changes and to consider their frequency, specificity and pathogenesis in congenital syphilis. A further purpose was to correlate the observations on the deciduous and on the permanent teeth. Many writers have taken exception to the opinions expressed by Hutchinson [1] since his original description of the specificity of the abnormalities in the upper permanent central incisors in congenital syphilis.

REVIEW OF THE LITERATURE

One of the earliest references to dental alterations in syphilis was that by Sanchez [2] in 1785. Hutchinson [1] in 1858 gave the first complete report and described several disturbances in dental development which he thought were due to congenital syphilis. Subsequently, however, he modified his view and conceded that dental dystrophies other than the Hutchinson incisor could be caused by other factors. According to Magitot [2] (1881), eclampsia was the important etiologic factor of hypoplasia of the enamel. In 1884 the abnormal state of the permanent first molar in congenital syphilis was described by Fournier [3] and by Moon.[4] Cavallaro's report [5] in 1908 was an extensive clinical and

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1. Hutchinson, J.: Tr. Path. Soc. London **9**:449; **10**:287, 1858.
2. Cited by Cavallaro.[5a]
3. Fournier, A.: Dent. Cosmos **26**:12, 81 and 141, 1884.

(Footnotes continued on next page)

histologic work. He and Stein [6] stated the belief that all types of dental hypoplasia are of syphilitic origin. Karnosh [7] and others [8] stated that the Hutchinson incisor is due to a deformity in the developmental lobes and is not an effect of transitory calcium deficiency (table). Extensive bibliographies are found in the reviews by Kranz [9] and Lebourg.[10]

MATERIAL AND METHOD

Material.—The present study was based on examinations of 133 consecutive patients in the children's syphilis clinic, Central Free Dispensary, Rush Medical College, the University of Chicago. In addition to children for whom a positive

Historical Review of Dental Studies in Congenital Syphilis

Author	Date of Publication	Observations and Contributions
Sanchez	1785	Premature caries (black decay of teeth)
Hutchinson	1858	Notched and tapered permanent upper central incisors as part of Hutchinson's triad
Fournier; Moon	1884	"Mulberry molar," constricted and irregular occlusal surface of permanent first molar
Cavallaro	1908	Extensive histologic and clinical studies; did not distinguish between changes in form of tooth and enamel formation and believed all were caused by congenital syphilis
Stokes and Gardner *	1923	Roentgenographic diagnosis of unerupted Hutchinson incisors
Pfluger	1924	"Bud molar," constricted but smooth occlusal surface of first permanent molar
Karnosh	1926	Tooth-forming organs not seriously impaired in utero but suddenly at birth; not a transitory calcium deficiency but a deformity of developmental lobes
de Jonge-Cohen	1932	Hutchinson tooth has aplasia of medial edge tubercle and convergence of both approximal crown surfaces
Sarnat, Schour and Heupel	1941	Roentgenographic diagnosis of unerupted Hutchinson incisors and mulberry molars plus disturbance in enamel formation due to systemic disease at a later time
Sarnat and Shaw (this report)	....	Correlation of dental development with conditions found in deciduous and permanent teeth

* Stokes, J. H., and Gardner, B. S.: J. A. M. A. **80**: 28, 1923.

diagnosis of congenital syphilis had been made, there were others who so far had shown no signs of the condition. The latter children were born of syphilitic

4. Moon, cited by Karnosh.[7]

5. Cavallaro, J.: Dent. Cosmos (*a*) **50**:1161 and (*b*) 1325, 1908; (*c*) **51**:16 and (*d*) 156, 1909.

6. Stein, J. B.: Dent. Cosmos **55**:691, 1913.

7. Karnosh, L. J.: Histopathology of Syphilitic Hypoplasia of Teeth, Arch. Dermat. & Syph. **13**:25 (Jan.) 1926.

8. (*a*) Jeans, P. C., and Cooke, J. V.: Prepubescent Syphilis, New York, D. Appleton & Company, 1930. (*b*) de Jonge-Cohen, T. E.: Nederl. tijdschr. v. geneesk. **76**:2208, 1932. (*c*) de Jonge-Cohen, T. E.: Arch. f. Dermat. u. Syph. **173**:388, 1936.

9. Kranz, P., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 19, p. 240.

10. Lebourg, L.: Les dystrophies dentaires de la syphilis héréditaire, Paris, Gaston Doin, 1939.

mothers (treated and untreated) and were being observed over a long period. Many of them were siblings of the children with congenital syphilis. There were also a few patients with acquired syphilis in the group.

Method.—Medical History and Physical Examination: In every instance a medical history was obtained and a physical examination performed. In selected cases roentgenograms of the long bones were taken. The blood serum of every patient and the spinal fluid of some were tested for syphilis.

Dental Analyses: The dental examination, performed without knowledge of the patient's medical diagnosis, consisted of:

Gross Examination with Dental Explorer and Mouth Mirror. A record was made of the particular teeth which varied morphologically from the normal and those which showed evidence of disturbed enamel formation in the form of hypoplasia of the enamel (chronologic enamel aplasia).

Roentgenograms. These were taken routinely of every patient whose permanent teeth were not yet erupted or whose erupted permanent teeth showed abnormal form. The roentgenograms provided a graphic record of the enamel, dentin and dentinoenamel junction of the various erupted and unerupted teeth and permitted a more complete study of the presence or absence of teeth. Roentgenograms were also taken of selected extracted teeth from normal patients and patients with congenital syphilis.

Photographs. Black and white and colored photographs of the teeth were taken of a selected group of patients for permanent record. In addition, photographs were taken of selected extracted teeth from normal patients and patients with congenital syphilis.

Impressions and Models. Hydrocolloid impressions of the dentures were taken in several instances. Models developed from the impressions served as valuable records.

Histologic Material. Midsagittal ground sections were made in the mesiodistal plane of selected extracted teeth. These were obtained from patients with and without congenital syphilis.

BRIEF SUMMARY OF DENTAL DEVELOPMENT

Since the dental effects in congenital syphilis are of developmental nature, they can be best understood if the important stages in dental development are first reviewed. These are: (1) growth, (2) calcification, (3) eruption and (4) attrition. For this purpose, only the first stage (growth) of the deciduous and permanent central incisors, which are comparable to the other deciduous and permanent teeth, will be considered. This stage can be further subdivided into initiation, proliferation, morphodifferentiation, histodifferentiation and apposition. Because the deciduous teeth develop earlier than the permanent teeth, they are in a later stage of development at any particular time in the life of the fetus or infant (fig. 1). Consequently, systemic disturbances will produce a different effect on growing deciduous teeth than on growing permanent teeth.

Initiation (Deciduous Incisor).—Between the sixth and seventh weeks of intrauterine life an inward proliferation of the oral epithelium (*O. ep.*) begins (fig. 1 *A*). This is the dental anlage (*D. a.*).

Proliferation (Deciduous Incisor).—Cellular proliferation continues until an invagination takes place and the connective tissue which borders the invaginated epithelial portion condenses and forms the dental papilla (*D. p.*), the primordium of the dentin and pulp (fig. 1 *B*).

Differentiation (Deciduous Incisor).—The enamel organ (*En. Org.*), which originates from the invaginated epithelium, gives rise to the inner enamel epithelium (*I. e. e.*). Two changes occur at this time:

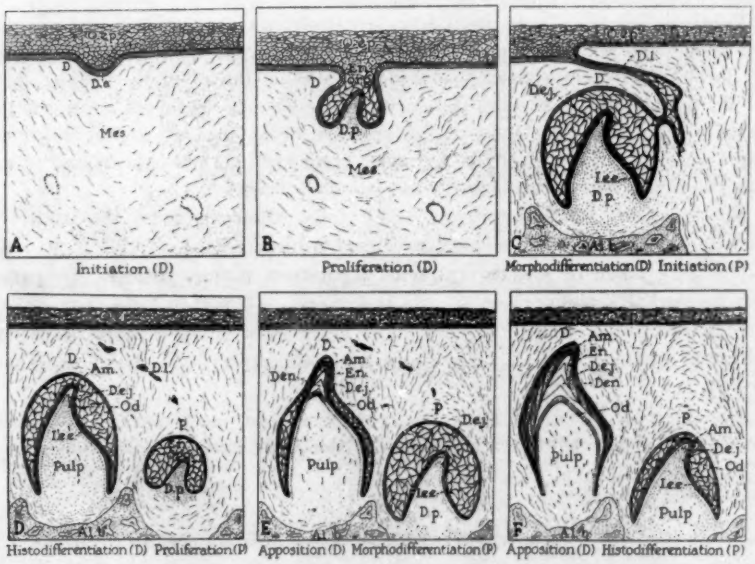

Fig. 1.—Diagrammatic representation of the development of the lower deciduous and permanent central incisors, showing: *D*, a deciduous tooth; *P*, a permanent tooth; *O.ep.*, oral epithelium; *D.a.*, dental anlage; *Mes.*, undifferentiated mesenchyme; *D.p.*, dental papilla; *En.Org.*, enamel organ; *I.e.e.*, inner enamel epithelium; *Dej.*, dentinoenamel junction; *D.l.*, dental lamina; *Den.*, dentin; *En.*, enamel; *Am.*, ameloblasts; *Od.*, odontoblasts, and *Al.b.*, alveolar bone.

1. Morphodifferentiation, the determination and differentiation of the dentinoenamel junction between the inner enamel epithelium and the adjacent connective tissue cells of the dental papilla (fig. 1 *C*). The dentinoenamel junction determines the basic pattern of the tooth. At about the time of this change (approximately the fourth month in utero), the initiation of the permanent incisor begins. 2. Histodifferentiation, the differentiation of ameloblasts (*Am.*) (enamel-forming cells) from the inner enamel epithelium, and of odontoblasts (*Od.*) from

the adjacent connective tissue of the dental papilla (fig. 1 *D*). This stage occurs about the fifth month in utero. The permanent tooth bud is undergoing proliferation.

Formation or Apposition of Enamel and Dentin (Deciduous Incisor).—The next stage is the formation of a cusp of dentin followed by a corresponding amount of enamel on the outer portion of the dentinoenamel junction. When this formation has been initiated, there is a synchronous recession of the ameloblasts and odontoblasts from each other. Incremental layers of enamel are apposed one on top of the other until the cusp is fully formed. Subsequent layers are apposed

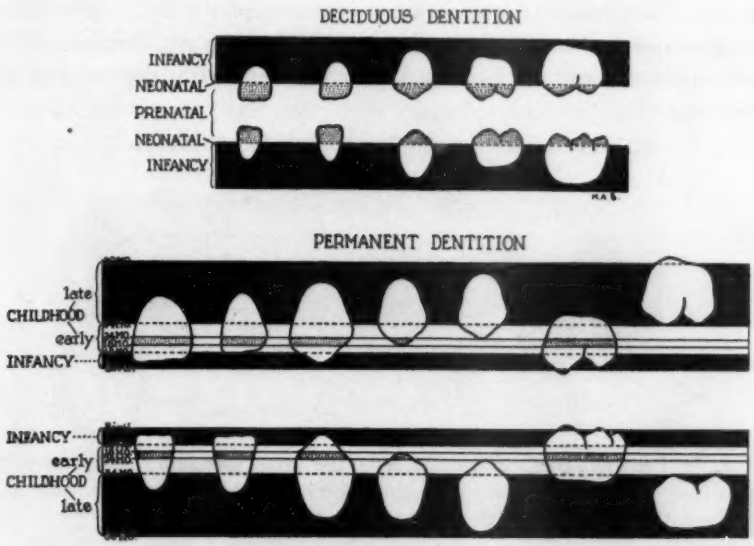

Fig. 2.—Diagrammatic representation of the chronologic development of the crowns of the deciduous and permanent teeth (from Sarnat and Schour [11b]).

at the sides until the crown is complete. The enamel is thickest at the incisal edge; it gradually tapers off and ends at the junction of the anatomic crown and root. For each layer of enamel that is apposed, outside the previous one, a corresponding layer of dentin is apposed, within the previous one. After formation of enamel has ceased, formation of dentin still continues to complete the root.

Comment.—This same developmental process, with certain variations, is initiated at definite intervals for the various teeth in both dentitions (fig. 2). At the time of birth the first molars and incisors of the permanent dentition (except the upper lateral incisors) are in the stage of morphodifferentiation, while the deciduous teeth are forming

enamel (fig. 1 *E*). The occurrence of a sufficiently severe systemic disturbance during development of the teeth may affect the particular stage in process at the time [11] and be expressed at a later date as one of the following dental dystrophies:

Stages in Growth	Dental Aberration
Initiation	Anodontia
Proliferation	Odontoma
Morphodifferentiation	Hutchinson incisor, Moon molar, peg-shaped teeth
Apposition	Hypoplasia of enamel (chronologic enamel aplasia)

Thus in congenital syphilis, because the form of the tooth is altered (morphodifferentiation), the primary requisite of the upper permanent central incisor and of the first permanent molar is a convergence of the lateral surfaces, with a resulting narrowed mesiodistal diameter of the crown (fig. 3).

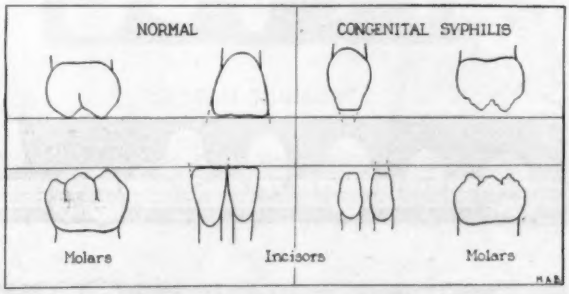

Fig. 3.—Diagrammatic representation of the gross morphologic characteristics observed in the teeth of a patient with congenital syphilis, compared with those of a normal control subject (from Sarnat, Schour and Heupel [18]).

OBSERVATIONS

Of the 133 patients examined there were 3 children with acquired syphilis and 17 who were classified as nonsyphilitic because they were born of mothers adequately treated during pregnancy and because they had shown no signs of congenital syphilis. Forty others who had shown no signs of congenital syphilis were under clinical observation because they were born of syphilitic mothers who had inadequate or no treatment during pregnancy. Finally, there were 73 children who had a

11. (*a*) Schour, I., and Massler, M.: J. Am. Dent. A. **27**:1778, 1940. (*b*) Sarnat, B. G., and Schour, I.: ibid. **28**:1989, 1941; **29**:67, 1942. (*c*) Brodie, A. G., and Sarnat, B. G.: Ectodermal Dysplasia (Anhidrotic Type) with Complete Anodontia: A Serial Roentgenographic Cephalometric Appraisal, Am. J. Dis. Child., to be published.

positive diagnosis of congenital syphilis and whose serum had reacted positively at some time.

Of the 73 children with congenital syphilis, there were 57 children 7 years of age or older whose permanent upper central incisors and first molars were erupted and examined clinically. Eighteen (32 per cent) had teeth which appeared to be characteristic of congenital syphilis. In a dental roentgen examination of the remaining 16 children with an unerupted permanent dentition, teeth with converging proximal surfaces, characteristic of congenital syphilis, were found in 4 patients (25 per cent). It is significant that in the groups of children whose condition was not diagnosed as congenital syphilis no child showed these characteristic dental changes.

Deciduous Teeth.—In the 4 patients who still had their deciduous teeth, there was hypoplasia of the enamel. The time of disturbed formation of enamel corresponded approximately with the neonatal period and the period of earliest infancy. The teeth, especially the

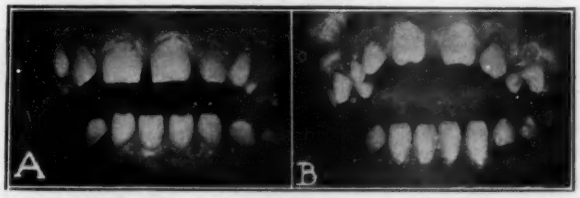

Fig. 4.—Intraoral photographs of patients with congenital syphilis and Hutchinson incisors. *A*, note in the upper central incisors the convergence of the proximal surfaces, the slight notch on the incisal edge and the diastema. This is the so-called screwdriver type. In the lower incisors, in addition to a convergence of the proximal surfaces, the notch on the incisal edge is more apparent. (See fig. 5 *A*.) *B*, note in the upper central incisors the convergence of the proximal surfaces in the incisal third of the crown, the distinct notch on the incisal edge and the diastema. In the lower incisors the convergence of the proximal surfaces is apparent; the notch on the incisal edge is not pronounced. (See fig. 5 *B*.)

central and lateral incisors, were badly worn and showed extreme caries. No disturbance in the morphologic pattern was seen.

PERMANENT TEETH.—*Incisors.*—Gross Observations: Two groups of permanent teeth were found to have a convergence of the proximal (lateral) surfaces, namely the incisors and the first molars. The teeth most frequently affected were the upper central incisors, usually both but sometimes only one. The morphologic pattern was extremely variable, and in several instances in which the distinction was not pronounced the teeth were considered normal. Twenty-two patients had Hutchinson incisors. The teeth of 14 of these patients had, in addition to a convergence of the lateral surfaces (fig. 4 *A*), a midincisal notch

(fig. 4 *B*). The notch varied from slight to deep. The lower central and lateral incisors also showed a convergence of the lateral surfaces and an incisal notch, or the former alone, but not so frequently as

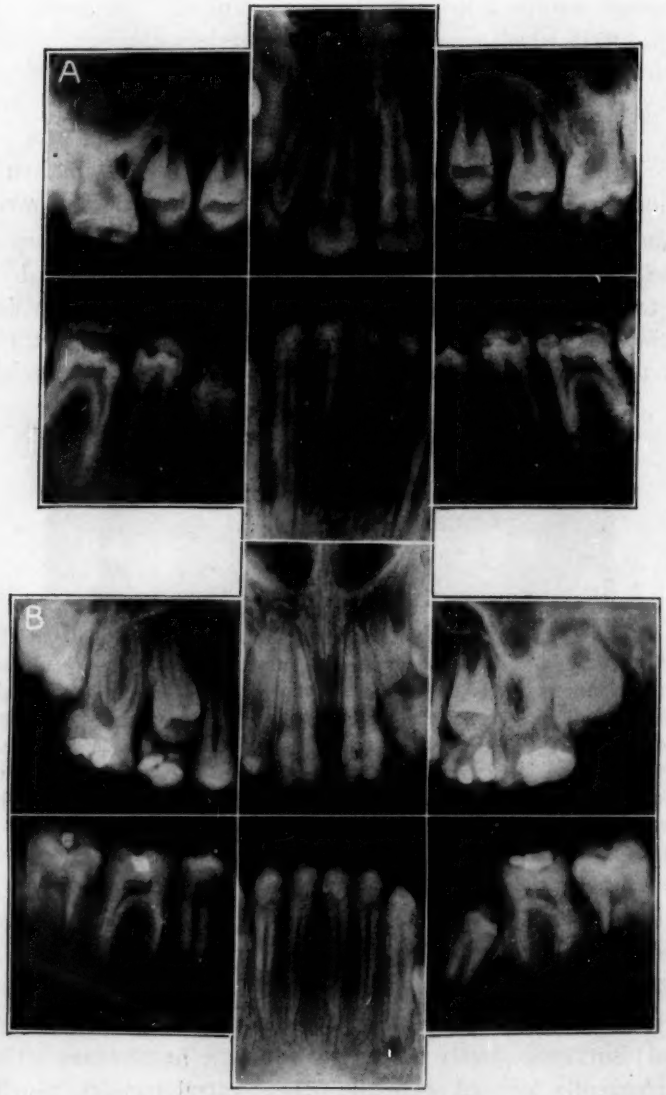

Fig. 5.—Intraoral roentgenograms of the ircisor and molar areas of the same patients with congenital syphilis described in figure 4. Note the size and shape of some of the permanent incisors (except the upper lateral incisors) and the permanent first molars. (See fig. 4.)

the upper incisors (fig. 4 *A* and *B*). The upper lateral incisor was conspicuous in that in only 1 instance did its pattern vary from the

normal. In some patients malocclusion and a diastema between the two upper permanent central incisors were found.

Roentgenographic Observations: A pronounced convergence in the mesiodistal diameter of the dentinoenamel junction of the affected teeth

Fig. 6.—Intraoral roentgenograms of patients with congenital syphilis, showing unerupted permanent central incisors and first molars. Note the convergence of the proximal surfaces and the smaller size of the teeth. *A*, the permanent central incisors are screwdriver-like; the permanent first molars are mulberry-like. Note the irregularity of the incisal third and the occlusal surface. *B*, note the notch in the unerupted permanent upper central incisors. The permanent first molars are the bud form described by Pfluger.

(up to about the midcervical level) was seen in the examination of the roentgenograms (fig. 5 *A* and *B*). In addition, the notched defect of the midregion of the incisal edge could readily be seen. The thickness of the enamel appeared to be normal. Examination of the unerupted teeth in the roentgenograms revealed characteristic Hutchinson incisors

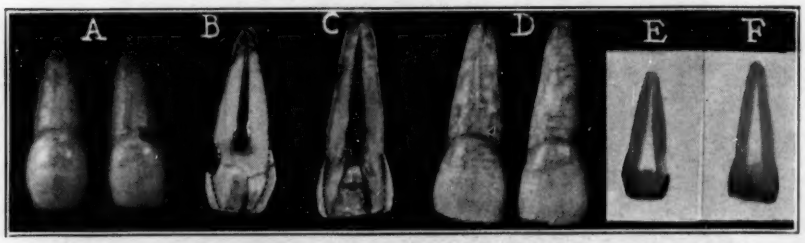

Fig. 7.—*A*, extracted Hutchinson incisors. Note convergence of proximal surfaces beginning at about the middle third of the crown, which gives it a screwdriver-like shape. *B*, mesiodistal ground section of a Hutchinson incisor. The significant histologic abnormality is the form of the dentinoenamel junction. *C*, mesiodistal ground section of a normal incisor. Compare the dentinoenamel junction with that in *B*. *D*, extracted normal incisors. Note the divergence of the proximal surfaces. *E* and *F*, roentgenograms of ground sections of the Hutchinson (*E*) and normal (*F*) incisors.

Fig. 8.—Extracted bud type and normal upper and lower first molars of second dentition. *A* and *B*, note difference in size and form in the buccal view of bud molars (*A*) and normal molars (*B*). *C* and *D*, mesiodistal ground sections of bud molars (*C*) and normal molars (*D*). The significant difference is in the outline of the dentinoenamel junction. *E* and *F*, note difference in size and form in the occlusal view of bud molars (*E*) and normal molars (*F*). *G* and *H*, roentgenograms of ground sections of bud molars (*G*) and normal molars (*H*).

in every instance in which the deciduous teeth had chronologic enamel aplasia (fig. 6 *A* and *B*).

Congenital absence of teeth (upper permanent lateral incisors) was noted in only 1 of 73 patients whose serum reacted positively for syphilis. This was confirmed by both gross and roentgen examinations.

Molars.—Gross Observations: The permanent first molars were not so consistently affected as were the central incisors. Here too, as in the incisors, the proximal surfaces were constricted so that approximately the occlusal third was narrower than normal. In addition, in some

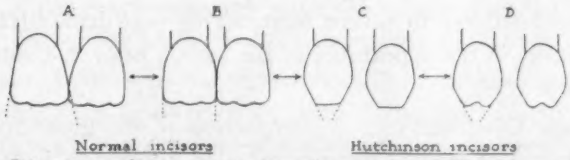

Fig. 9.—Diagrammatic representation of normal and Hutchinson incisors.

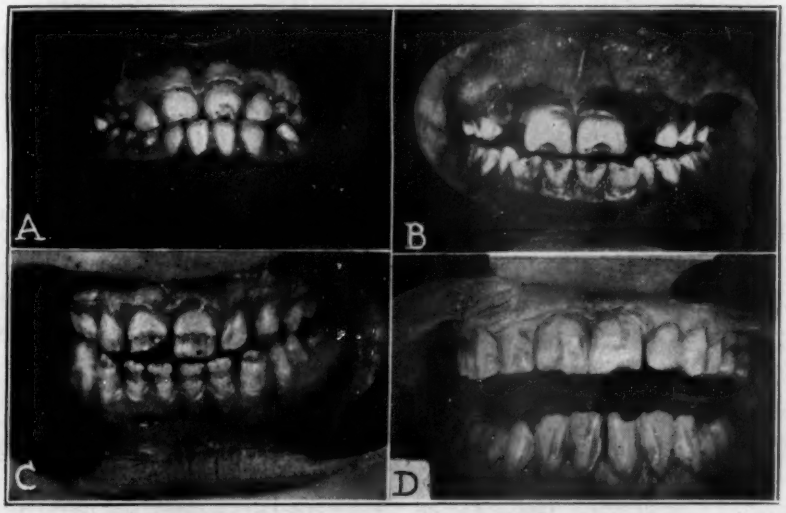

Fig. 10.—Differential diagnosis of the Hutchinson incisor. *A*, typical Hutchinson incisors, with convergence of the proximal surfaces and a notch of the mid-incisal edge. This was caused by a disturbance in dental development at about birth and shortly thereafter. *B*, notched incisors due to lack of enamel formation (hypoplasia of enamel). This abnormality was caused by a disturbance in dental development when the child was about 3 to 4 months of age. *C*, hypoplasia of the enamel due to a systemic disturbance between approximately 6 and 12 months of age. *D*, notched incisors due to environmental rather than developmental factors (abnormal local wear of teeth [abrasion] due to repeated holding of nails between teeth by an upholsterer). The only lesion characteristic of and due to congenital syphilis is that shown in *A*.

molars hypoplasia of enamel (chronologic enamel aplasia) was superposed. Of the 88 possible molars in the 22 patients with Hutchinson

teeth, only 11 were diagnostic (6 patients); 27 were either absent or so carious that they were of no diagnostic value; 40 appeared to be normal, and 10 had hypoplasia of enamel but no distortion of the crown.

Roentgenographic Observations: Roentgenographic examination revealed the convergence of the sides of the molars and irregular enamel in certain instances. This was also diagnosed prior to eruption (fig. 6 *A* and *B*). It is interesting to note that the occlusal surfaces after eruption were subject to severe wear. This was demonstrated roentgenographically in the appearance of the molars prior and subsequent to occlusal wear.

Histologic Observations: A comparison of the ground sections of Hutchinson and of normal incisors revealed differences in the size and form of the dentinoenamel junctions but no significant structural differences in the enamel and dentin. The dentinoenamel junction was smaller and constricted in about the incisal third of the crown (fig. 7). Similar conditions were found in the molars (fig. 8).

COMMENT

Systemic Disease and Growing Teeth.—Recent clinical studies [11a, b] have demonstrated the growing tooth to be an accurate permanent chronologic recorder of metabolic disturbances. The various stages of dental development occur in sequence at a definite time for each tooth. With the knowledge of the chronology of development, the time of the systemic disturbance, but not the etiologic factor, can be determined. The amount of dental development at birth is dependent in part on the maturity of the infant. Thus a 7 month premature infant will not have as fully developed a dentition as a full term newborn infant. The first permanent molars show evidence of tooth formation and calcification at birth. The anterior teeth, except the upper lateral incisors, develop a little later and show no evidence of calcification until about the third month after birth (fig. 2).

The effects of systemic disease on growing teeth have been reported.[11a, b] Schour [12] has demonstrated the neonatal line in the teeth in the process of development at the time of birth. The separation of the normal fetus from its placental circulation and the adjustments made during the neonatal period by the infant are severe enough to be recorded in the teeth. The infant who, in addition, has to contend with a syphilitic infection at that time may register the effects of this

12. Schour, I.: J. Am. Dent. A. **23**:1946, 1936.

more severe disturbance in the portions of the deciduous and permanent teeth actively developing at that particular time.[13]

However, it should be pointed out that the clinical course of the infant and the dental conditions cannot always be correlated. Thus there were several patients who had a history of florid syphilis but no characteristic changes in the teeth. Others had a history of a relatively undisturbed postnatal life but nevertheless had abnormal dental development. Consequently, the Hutchinson incisor and the bud or mulberry molar should not necessarily be considered indicative of the severity of the disease during the neonatal and infancy periods.

Deciduous Teeth.—In the patients studied, the anterior deciduous teeth had been shed or were badly worn. The posterior teeth showed aplasia of enamel characteristic of a disturbed development during the neonatal and earliest infancy periods. These observations were consistent with those of Karnosh.[7] No changes in the morphologic pattern were seen. This was explained on the basis that morphodifferentiation and the dentinoenamel junction were determined in utero, before any severe systemic disturbance affected the teeth (fig. 1 *C*). The disturbance in enamel formation (hypoplasia of the enamel) was not pathognomonic of either congenital syphilis or any other disease.[11b]

Permanent Teeth.—Incisors: The normal permanent upper central incisors are subject to considerable morphologic variation. Generally, however, the crown has the form shown in figure 9 *A*. The three mamelons on the incisal edge are remnants of the developmental lobes. These are worn soon after the teeth are in occlusion (6 to 9 years).

The permanent upper central incisors in children with congenital syphilis begin to undergo morphodifferentiation at about birth (fig. 1 *E*). The first evidence is the three lobes, the middle one of which may be more affected than the two lateral lobes. According to De Jonge-Cohen,[8b, c] there may be an aplasia of the median lobe. Concomitant with this, the lateral lobes may be smaller and closer together.[7] These factors produce a narrowed and constricted dentinoenamel junction. The extent of the deformity is dependent on the degree of aplasia of the central lobe and usually involves only the incisal third of the tooth. It is on this distorted dentinoenamel junction, which determines the future morphologic form of the tooth, that normal enamel is laid down.

Pitts [14] has classified the various types of Hutchinson teeth and has shown the difficulty which may be encountered in deciding whether a tooth has normal morphologic characteristics or not. Because the

13. Footnotes 5, 7, 8 and 9.

14. Pitts, A. T.: Proc. Roy. Soc. Med. **20**:1531, 1927.

degree of convergence of the lateral surfaces may vary, the diagnosis may sometimes be questionable (fig. 9 *B*). The primary requisite of the Hutchinson incisor is the convergence of the proximal surfaces, with a resulting narrowed mesiodistal incisal diameter of the crown (fig. 9 *C*). In addition to the screwdriver-like effect of the tooth, a central notch may be present on the incisal surface (fig. 9 *D*). Contrary to the views of some writers, this notch is present before the tooth appears in the oral cavity (fig. 6 *B*). However, with occlusion, the tooth structure, which may be fragile in the central portion of the incisal region, may wear, and the notch may become accentuated.

The permanent lower central incisors may also appear morphologically similar to the permanent upper central incisors (fig. 4), but the abnormal forms do not appear so frequently. The cuspids (canines) are seldom involved. This is probably due to the fact that these teeth usually develop somewhat later. The permanent upper lateral incisors are not affected, because they do not begin development until a much later time (at about 10 months).

Molars: The permanent first molars have also been described as showing characteristic abnormalities in congenital syphilis.[15] The cusps are generally crowded together on a crown surface of dwarfed dimensions. In normal patients and patients with congenital syphilis the average mesiodistal diameter of the permanent first molar at the cuspal level was found to be 13.4 and 8.3 mm. respectively.[16] Karnosh [7] expressed the opinion that the incisor arose from a diminutive enamel organ but failed to attribute the molar to the same source. However, his illustrations clearly showed a dentinoenamel junction which was narrower than normal in the occlusal region. This narrowed dentinoenamel junction, as in the permanent central incisor, was produced at the time of morphodifferentiation. Subsequently enamel was apposed on this abnormal pattern. Pfluger [16] called this the bud form molar, because it gave the impression that the crown had not been fully outfolded (fig. 6 *B* and 8 *A*). In addition, enamel formation was sometimes affected, and aplasia of the enamel occurred for the particular period (fig. 6 *A*). This caused an irregular occlusal area, and for this reason the tooth had been called the mulberry molar (also Moon or Fournier molar).

Thus the teeth which are affected and may be of diagnostic value in congenital syphilis are the permanent upper central incisors, lower central and lateral incisors and first molars (fig. 3).

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15. Fournier.[3] Moon.[4] de Jonge-Cohen.[5b,c] Pfluger.[16]

16. Pfluger, H.: München. med. Wchnschr. **71**:605, 1924.

Specificity and Differential Diagnosis.—Hutchinson [1] described dental conditions which he believed to be pathognomonic of congenital syphilis. His views, however, were questioned by Magitot,[2] Black [17] and others.[2] It is important at this time to recall that in congenital syphilis the dentinoenamel junction is dwarfed in the permanent upper central incisors and first molars. Consequently the crown is smaller. This should not be confused with hypoplasia of the enamel (chronologic enamel aplasia) (fig. 10 *C*), which is a disturbance not in the outline of the dentinoenamel junction but in the enamel formation. Hypoplasia occurs at a later time and may be caused by rickets, hypoparathyroidism or fluorosis. The combination of the Hutchinson incisor and hypoplasia of the enamel, though rare, does occur (fig. 6 *A*).[18] Pfluger [16] emphasized that in congenital syphilis one deals not with hypoplasia of the enamel but with the changed form of the entire tooth. If the hypoplasia occurred early, so that the enamel on the incisal edge was missing, the incisor would have a notched appearance (fig. 10 *B*). The dentinoenamel junction, however, is not affected. In addition, not all Hutchinson incisors are notched (fig. 4 *A*). For these reasons, the notched incisor alone should not be used as a means of diagnosis.

Congenital syphilis is unique as a systemic disease already present at the time of birth and often producing a severe and continued malnutrition in earliest infancy. This is an added disturbance, with which the newborn infant must cope. Thus morphodifferentiation of those permanent teeth active at the time may be affected, although the severity of the disease cannot always be correlated with the dental condition. Karnosh [7] stated that the tooth-forming organs were not seriously impaired in utero and that most of the deciduous teeth as well as the prenatal caps of the first permanent molars were fairly well formed in spite of the presence of active syphilis in the fetus. The disease has a rather precipitous effect on the active enamel organ as soon as the infant is separated from the placental circulation.

Black [17] did not question that the Hutchinson incisor was distinctly different from teeth with hypoplasia of enamel. He did believe, however, that any systemic disease which might be present at the same time might give the same result. Nevertheless, in a previous clinical study of dental dystrophies,[11b] the Hutchinson incisor or Moon molar was not demonstrated without the presence of congenital syphilis. Because

17. Black, G. V.: Diseases of Hard Tissues of the Teeth, Chicago, Medico-Dental Publishing Company, 1924, vol. 1, p. 1.

18. Sarnat, B. G.; Schour, I., and Heupel, R.: Roentgenographic Diagnosis of Congenital Syphilis in Unerupted Permanent Teeth, J. A. M. A. **116**:2745 (June 21) 1941.

congenital syphilis is active at the time of birth, teeth which are growing will be affected in the developmental processes proceeding at the time. Since no other comparable severe systemic disturbance which will cause the Hutchinson incisor is known at the present time, this tooth may be considered to be pathognomonic for congenital syphilis. However, it would be valuable to study the teeth of patients who had a severe disturbance, like tuberculosis, pyloric stenosis or diarrhea, during the neonatal and infancy periods. Thus, Wolfe [19] and Schour and Kronfeld [20] have reported cases of hypoplasia of the enamel of the deciduous teeth due to rickets and an injury of the brain which occurred during the prenatal and neonatal periods respectively. There was no history of syphilis. If the permanent teeth had a narrowed dentinoenamel junction, the effect of syphilis on the teeth would not be specific.

In partial anodontia, arachnodactylia, facial hemiatrophy, mongolian idiocy, achondroplasia and a few other conditions, the upper permanent incisors may have a narrowed dentinoenamel junction and a peg shape. Whereas the incisal third is affected in a Hutchinson incisor, the entire crown is affected and other teeth show similar disturbances, which cannot be correlated on a chronologic basis with events during the neonatal period and earliest infancy. With a little practice and experience, on examining the dentition of a child one can unmistakably determine whether it belongs to an idiot or to a child with hereditary syphilis.[5] Furthermore, these malformations should be distinguished from the semilunar notch frequently seen in the incisors of upholsterers and carpenters, who keep nails between their teeth (fig. 10 *D*).[21]

Absence of Teeth.—Another condition which has been reported in congenital syphilis is the absence of few or many teeth. This has been questioned.[22] It is important to differentiate between congenitally absent, unerupted and extracted teeth. In only 1 of this series of patients were the permanent upper lateral incisors absent. Intraoral roentgenograms did not show their presence in the jaw; there was no history of extraction. This patient, moreover, did not have typical Hutchinson incisors. The absence of teeth (anodontia), partial or complete, is probably on a hereditary basis.[11c]

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19. Wolfe, J. J.: Teeth in Fetal Rickets, Am. J. Dis. Child. **49**:905 (April) 1935.

20. Schour, I., and Kronfeld, R.: Tooth Ring Analysis: Neonatal Dental Hypoplasia; Analysis of Teeth of Infant with Injury of Brain at Birth, Arch. Path. **26**:471 (Aug.) 1938.

21. Schour, I., and Sarnat, B. G.: Oral Manifestations of Occupational Origin, J. A. M. A., to be published.

22. Stathers, F. R.: Am. J. Orthodontics **28**:138, 1942.

No particular type of malocclusion occurred with sufficient frequency to be considered characteristic of congenital syphilis, although the open bite was common.[23]

Value of Roentgenograms.—Because clinically the Hutchinson incisor is seen only after the child is 7 years of age, when the incisors erupt into the oral cavity, it has been mistakenly regarded as a symptom of late congenital syphilis. It is only a late manifestation of an early effect. By means of intraoral roentgenograms, the unerupted screwdriver-shaped permanent incisor has been demonstrated as early as the second to the fourth year of life (fig. 6).[18]

Roentgenograms of the unerupted teeth should be taken routinely with those of bone. Studies of bone are an aid in the early diagnosis of congenital syphilis, but Caffey[24] cautioned that such studies are rarely conclusively diagnostic. Bone, moreover, is subject to resorption and apposition, and the observations are subject to change, especially after treatment. Teeth are not subject to resorption, and the specific findings are permanent. Jeans and Cooke[8a] stated that in general the dental deformities constitute the most important of the stigmas of congenital syphilis on account of their relative frequency. To this statement two other characteristics should be added, namely, the early occurrence and the permanency of the dental dystrophy.

Roentgenographic examination of these teeth is also of value because the true form of the dentinoenamel junction can be determined. Further, because the enamel is wider at the incisal edge than at the cementoenamel junction, the convergence is more pronounced at the dentinoenamel junction than on the proximal surfaces (fig. 5). In a recent study of congenital syphilis,[23a] it was found that a greater number of dental stigmas were observed by means of roentgenograms than clinically.

SUMMARY AND CONCLUSIONS

A group of 73 patients with congenital syphilis were studied. Twenty-two (30 per cent) had dental changes characteristic of this disease.

Congenital syphilis, a systemic disease which is exacerbated during the neonatal period and infancy, may affect the particular stage of tooth development active at the time. The effects are different in the growing deciduous and permanent teeth. The deciduous teeth, active in the formation of enamel, show developmental disturbances in that structure

23. (*a*) Johnston, W. D.; Anderson, B. G., and McAlenney, P. F.: Am. J. Orthodontics **27**:667, 1941 (*b*) Stathers.[22]

24. Caffey, J.: Am. J. Roentgenol. **42**:637, 1939.

(chronologic enamel aplasia); the permanent teeth, active in morphodifferentiation, show a disturbance of the dentinoenamel junction, with a resulting characteristic dwarfing of the crown.

Consequently, the convergence of the proximal (lateral) surfaces of the permanent upper central incisors (Hutchinson) and molars (Moon, Fournier, Pfluger) should not be confused with disturbances of enamel formation (hypoplasia of the enamel) which occurred at a later time.

However, no correlation was made between the severity of the disease in the neonatal period and earliest infancy and the dental development.

These developmental disturbances of the teeth are permanent and have been found only in congenital syphilis. They can be demonstrated roentgenographically prior to eruption.

Dr. James S. Gold assisted in the clinical part of this study.

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STUDIES ON BLOOD PHOSPHORUS

III. INTRACELLULAR AND EXTRACELLULAR BLOOD PHOSPHORUS IN ANEMIA IN CHILDREN AND IN EXPERIMENTAL ANEMIA

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Few facts are available concerning the distribution of phosphorus in the blood of patients with anemia. The most remarkable contribution was made by Farmer and Maizels,[1] who found an enormous increase of the acid-soluble fraction in microcytic hypochromic anemia in adults. Their conclusions are of considerable theoretic interest and will be analyzed later. The results of other investigators (Warweg and Stearns,[2] Euler and Brandt,[3] Kinzel,[4] Kirk [5]) are less conclusive but give the impression that some peculiar changes in the distribution of phosphorus may be present in anemic conditions. Of these publications only those of Warweg and Stearns [2] and Kinzel [4] refer to the organic blood phosphorus. To my knowledge the only estimate of the partition of organic phosphorus in anemic children has been made by Kinzel. I studied the extracellular and intracellular blood phosphorus in different forms of anemia in childhood. In addition, I investigated a few cases of experimental anemia in rabbits. As in some cases of Kinzel's investigation, the method of Lohmann and Nissen was employed, since in previous investigations [6] I confirmed its value in the analysis of the phosphorus partition.

From the Pediatric Laboratory and the Department of Pediatrics, New York Post-Graduate Medical School and Hospital, Columbia University.

1. Farmer, S. N., and Maizels, M.: Organic Anions of Human Erythrocytes, Biochem. J. **33**:280, 1939.

2. Warweg, E., and Stearns, G.: The Partition of Phosphorus in Blood in Relation to the Corpuscle Volume, J. Clin. Investigation **13**:411, 1934.

3. Euler, H., and Brandt, K. M.: Phosphate und Phosphatstoffwechsel in roten Blutzellen, Ztschr. f. physiol. Chem. **240**:215, 1936.

4. Kinzel, B.: Das Verhalten der Phosphorfractionen der Erythrocyten bei Anämie, Ztschr. f. Kinderh. **59**:160, 1937.

5. Kirk, E.: The Concentration of the Individual Phosphatides (Ether-Insoluble Phosphatide, Lecithin and Kephalin), and of Cerebrosides in Plasma and Red Blood Cells in Normal Individuals and in Pernicious Anemia, Acta med. Scandinav., 1938, supp. 89, p. 198.

6. Behrendt, H.: Studies on Blood Phosphorus: (*a*) I. Intracellular and Extracellular Blood Phosphorus, Am. J. Dis. Child. **64**:55 (July) 1942; (*b*) II. Blood Phosphorus Partition in Tetany and Guanidine Poisoning, ibid. **64**:475 (Sept.) 1942.

METHODS

The phosphorus fractions (inorganic phosphorus, phosphorus from pyrophosphate, hexose phosphates and glycerophosphate and acid-soluble and total phosphorus) were determined according to the method of Lohmann and Nissen, as described in a previous article.[6a] It may be recalled that the organic phosphorus is contained only in the erythrocytes and that it is possible to calculate the intracellular concentration of the different phosphorus fractions from the analytic data obtained by the method used.

From 6 to 10 cc. of oxalated venous blood was used. The corpuscle volume was determined by the hematocrit method. The intracellular ester phosphorus was calculated both as a unit of weight (milligrams per hundred cubic centimeters) and as mean corpuscular concentration (Wintrobe[7]). The same was done for hemoglobin. In some instances the phosphorus ester: red blood cell ratio was determined according to the method of Guest and Andrus.[8]

ANEMIA IN CHILDREN

Seven cases of anemia of different causation in children from 1½ to 13 years of age were investigated. The disease was hypochromic or normochromic in 5 patients and hyperchromic in cases 5 and 7. The highest reticulocyte count was 4.2 per cent (table 1, case 3); the highest normoblast count was 21 per cent (case 3). The presence of hemolysis was proved only in case 5. The white cell count was high in two instances (case 5, 14,400, case 6, 61,300). It can be taken for granted that a high white blood cell count affects the concentration of lipid or of nucleic acid phosphorus in the whole blood. Theoretically that could be expected in case 6, a case of leukemia. The patient in case 7, the other case of leukemia, was in the aleukemic stage at the time of investigation.

The blood counts of all the patients are contained in table 1.

The results of the chemical analyses of their blood are shown in table 2 and chart 1.

The amount of inorganic phosphorus in the whole blood was within the normal range for the age of the child in all cases except 5a and 7, in which it was increased above the normal average (plus 1 mg. and plus 2.7 mg. per hundred cubic centimeters, respectively). The average value in all 7 was 4.6 mg. per hundred cubic centimeters, while the normal average was 4.5 mg.

The organic ester phosphorus in the whole blood, comprising that from pyrophosphate, from hexose phosphates and from glycerophosphate,

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7. Wintrobe, M. M.: The Size and Hemoglobin Content of the Erythrocytes, J. Lab. & Clin. Med. **17**:899, 1932.

8. Guest, G. M., and Andrus, W.: Chemical Studies of the Blood in High Intestinal Obstruction: I. The Distribution of Phosphorus and Intracellular Changes, J. Clin. Investigation **11**:455, 1932.

TABLE 1.—*Blood Counts of Seven Children with Anemia*

Case	Red Blood Cells, Millions per Cu. Mm.	Hemoglobin, Gm./100 Cc.	Hemoglobin, per Cent	Color Index *	Platelets	White Blood Cells	Neutrophils	Lymphocytes	Eosinophils	Monocytes	Basophils	Reticulocytes	Normoblasts	Icteric Index
1	1.90	5.1	36.9	0.97	252,000	6,150	71	26	0	3	0	0	7.0	...
2	3.40	8.0	57.9	0.85	200,000	4,800	43	42	0	14	1	1	4.0	...
3	4.01	6.0	43.5	0.54	210,000	14,400	40	53	5	2	0	4.2	21.0	9.3
4	3.71	9.9	71.7	0.97	.....	.....	60	35	1	4	..	2.2	1.0	6.5
5a	1.64	5.8	42.0	1.28	.....	5,000	45	50	1	4	..	2.4	6.0	18.8
5b	2.27	8.0	57.9	1.28	150,000	4,850	38	56	..	5	1	2.2	1.0	13.6
6	1.25	3.2	23.1	0.92	82,000	61,300	53	36	..	10	..	0.8	19.0	...
7	0.83	2.4	18.3	1.10	82,000	400	12	86	2	0	0	...	...	...

* Thirteen and eight-tenths grams of hemoglobin was employed as 100 per cent.

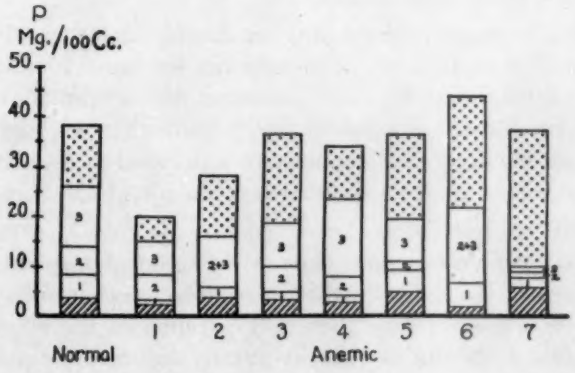

Chart 1.—Phosphorus fractions in whole blood in 7 cases of anemia in children. (The same cases represented in table 1 and table 2.) Hachure represents inorganic phosphorus; white, ester phosphorus (*1*, from pyrophosphate; *2*, from hexose phosphates; *3*, from glycerophosphate), and dots, lipid phosphorus.

was found to be definitely decreased. The range of values was from 3.6 to 19.5 mg. per hundred cubic centimeters, with an average of 13.3 mg., as against the normal average of 21.0 mg. The lowest concentration of ester phosphorus was present in the case of the severest anemia (case 7). In all other cases the reduction of ester phosphorus was moderate or negligible. A low content of ester phosphorus never occurred in mild anemia. The ester fractions affected most in anemia were the pyro ester and the hexose esters, whereas the glycerophosphate showed the smallest degree of reduction, with a range from 6.1 to 14.8 mg. of phosphorus per hundred cubic centimeters in cases 1 to 6. Only in case 7 was the extreme anemia associated with almost complete disappearance of glycerophosphate. The normal average is about 11.7 mg. per hundred cubic centimeters. In cases 4 and 6 the glycerophosphate phosphorus exceeded the normal average.

The last column of table 2 shows the ratio of the concentration of ester phosphorus to the red blood cell count (Guest and Andrus[8]), expressing the ester phosphorus in milligrams times 10^{-5} per million red blood cells.

The lipid phosphorus content, calculated as the difference between the total and the acid-soluble phosphorus, appeared to be irregular, ranging from very low amounts (5.1 mg. per hundred cubic centimeters) to values as high as 22.2 and 26.1 mg. in the 2 cases of leukemia. It is evident that both these cases must be excluded when the relation between lipid phosphorus and anemia is considered. The present results reveal only that the lipid fraction has no constant relation to the rest of the phosphorus fractions or to the severity of the anemia.

The concentration of nucleic acid phosphorus cannot be determined by the method used in these studies.

The total phosphorus content was remarkably stable in all 7 cases, ranging from 20.0 to 44.0 mg. of phosphorus per hundred cubic centimeters. The average was 33.3 mg., compared with a normal average of 39.0 mg. If the 2 cases of leukemia are discarded, an average amount of 30.6 mg. per hundred cubic centimeters was found in 5 patients with anemia. That means an average decrease of the total phosphorus by one fourth of the normal average.

Since the organic ester compounds of the blood phosphorus are virtually contained in the red cells, the intracellular concentration of these esters is more significant than their concentration in the whole blood. When calculated according to methods already outlined, the phosphorus concentration within the erythrocytes was found to be as shown in table 2.

The average and the range of inorganic phosphate content in 3 cases (2, 3 and 5a) were 6.1 mg. per hundred cubic centimeters of red cells and 2.2 to 9.2 mg. The normal average, as established in a previous report,[6a] is 4.7 mg. per hundred cubic centimeters. That means an average rise of 1.4 mg. of inorganic phosphorus in 100 cc. of red cells of anemic blood. Again the case of extreme leukemic anemia (case 7) must be discarded. In that case there was an intracellular concentration of inorganic phosphorus of 36.7 mg. per hundred cubic centimeters.

The ester phosphorus of the red cells ranged from 49.6 to 118.1 mg. of phosphorus per hundred cubic centimeters of cells, with an average of 68.7 mg. The normal average is 45.0 mg. It must be concluded that in anemia in childhood the intracellular organic ester phosphorus is definitely increased. This was true even in the case of severe leukemic anemia with an inorganic phosphorus content of 36.1 mg. per hundred cubic centimeters of cells. Although this enormous amount of inorganic phosphorus probably was derived from the organic esters, the accumulation of intact esters was greater than normal.

To visualize the accumulation of organic phosphates in the erythrocytes, it is preferable to calculate the mean corpuscular ester phosphorus, or the average amount by weight of intracellular ester phosphorus, which is analogous to the mean corpuscular hemoglobin (Wintrobe [7]). In addition, the mean corpuscular acid-soluble phosphorus was calculated.

TABLE 2.—*Phosphorus Fractions in Whole Blood and Erythrocytes in 7 Cases of Anemia in Children*

Case and Date	Diagnosis and Age	Red Blood Cells, Millions per Cu. Mm.	Hemoglobin, Gm. per 100 Cc.	Corpuscular Volume, per Cent		Inorganic phosphorus, Mg. per 100 Cc.	Phosphorus (Mg. per 100 Cc.) from: Pyrophosphate	Hexose Phosphates	Glycerophosphate	Acid-Soluble Phosphorus, Mg. per 100 Cc.	Ester Phosphorus, Mg. per 100 Cc.	Total Phosphorus, Mg. per 100 Cc.	Ratio of Ester Phosphorus to Red Blood Cells *
1	Nutritional	1.9	5.1	24	Whole blood	3.0	1.1	4.7	6.1	14.9	11.9	20.0	6.3
4/2/40	anemia; 3 yr.				Erythrocytes	...	4.6	19.6	25.4	....	49.6	....	...
2	Secondary	3.4	8.0	22	Whole blood	4.8	1.4	1.6	8.3	16.1	11.3	27.5	3.3
7/5/40	anemia; neuro-				Plasma	3.4	...	...	...	....	....	....	...
	blastoma; 2½ yr.				Erythrocytes	9.2	6.3	7.2	37.9	60.6	51.4	77.7	...
3	Erythroblas-	4.0	6.0	26	Whole blood	4.2	1.5	4.4	8.9	19.0	14.8	35.9	3.7
7/12/40	tic anemia;				Plasma	4.9	...	...	...	....	....	....	...
	1½ yr.				Erythrocytes	2.2	5.8	16.9	34.2	59.1	56.9	....	...
4	Sickle cell	3.7	9.9	26	Whole blood	3.3	1.5	3.2	14.8	22.8	19.5	33.5	5.3
8/24/40	anemia; 13 yr.				Erythrocytes	...	5.8	12.3	56.9	....	75.0	....	...
5a	Blood dys-	1.6	5.8	18	Whole blood	6.0	3.5	0.9	9.2	19.6	13.6	36.0	8.5
9/3/40	crasia; 2 yr.				Plasma	5.8	...	...	...	....	....	....	...
					Erythrocytes	6.9	19.4	5.0	51.1	82.4	75.5	....	...
5b	Blood dys-	2.2	8.0	21	Whole blood	5.5	...	...	10.4	18.7	13.2	....	6.0
9/13/40	crasia; 2 yr.				Erythrocytes	...	...	...	49.5	....	62.9	....	...
6	Leukemic	1.2	3.2	16	Whole blood	2.9	4.5 †		14.4	21.8	18.9	44.0	15.8
3/19/41	anemia; 2 yr.				Erythrocytes	...	28.1 †		90.0	....	118.1	....	...
7	Leukemic	0.8	2.4	6	Whole blood	6.7	1.6	1.0	1.0	10.3	3.6	36.4	4.5
7/14/41	anemia; 8 yr.				Plasma	4.8	...	...	...	....	...	23.5	...
					Erythrocytes	36.7	26.7	16.7	16.7	96.8	60.1	....	...
Average in anemia.....		2.4			Whole blood	4.6	1.4	2.6	9.1	17.9	13.3	33.3	6.7
Average normal.....		4.9			Whole blood	4.5	4.7	4.6	11.7	25.5	21.0	39.0	4.3

* The ratio of ester phosphorus to red blood cell count gives the ester phosphorus in milligrams × 10^{-5} per million red blood cells.

† This figure represents the sum of pyrophosphate and hexose phosphate phosphorus.

From table 3 it becomes evident that only in 2 cases (2 and 3) did the intracellular acid-soluble phosphorus approach the normal average amount of 0.0520 micromicrogram. In all the other cases there was a pronounced increase, ranging from 18.5 to 249.4 per cent. In the case of hemolytic anemia with hyperchromia (case 5), when the hemoglobin content was low the red cells carried 135 per cent more acid-soluble

phosphorus than normally. Ten days later, with the anemia less severe, the surplus of corpuscular acid-soluble phosphorus was only 63.5 per cent.

After comparison of the hemoglobin concentration of the blood (grams per liter) with the mean corpuscular acid-soluble phosphorus, it can be stated that in most instances a low hemoglobin concentration was associated with a high value for intracellular organic or acid-soluble phosphorus, and vice versa. There seems to exist a relationship between the hemoglobin concentration of the blood and the amount of organic ester phosphorus in the red cells, but the number of cases is too small to permit defining it. The mean corpuscular hemoglobin and the mean corpuscular ester phosphorus are not correlated in any way.

TABLE 3.—*Average Amount of Weight of Hemoglobin, Ester Phosphorus and Acid-Soluble Phosphorus in the Red Cells of 7 Anemic Children*

Case	Red Blood Cells, Millions per Cu. Mm.	Packed Red Cells, Cc. per Liter	Mean Corpuscular Volume, Cu. Microns	Hemoglobin, Gm. per Liter	Mean Corpuscular Hemoglobin, Gm.	Ester Phosphorus, Whole Blood, Gm. per Liter	Acid-Soluble Phosphorus, Whole Blood, Gm. per Liter	Mean Corpuscular Ester Phosphorus, Gm.	Mean Corpuscular Acid-Soluble Phosphorus, Gm.	Change in Percentage of Normal Average
1	1.9	240	126	57	30.0×10^{-12}	0.119	0.149	0.0626×10^{-12}	0.0784×10^{-12}	+ 50.8
2	3.4	220	65	80	23.5×10^{-12}	0.113	0.161	0.0332×10^{-12}	0.0474×10^{-12}	— 8.8
3	4.0	260	65	60	15.0×10^{-12}	0.148	0.190	0.0370×10^{-12}	0.0475×10^{-12}	— 8.7
4	3.7	260	70	99	26.8×10^{-12}	0.195	0.328	0.0527×10^{-12}	0.0616×10^{-12}	+ 18.5
5a	1.6	180	112	58	36.3×10^{-12}	0.136	0.196	0.0850×10^{-12}	0.1225×10^{-12}	+135.6
5b	2.2	210	95	80	36.4×10^{-12}	0.132	0.187	0.0600×10^{-12}	0.0850×10^{-12}	+ 63.5
6	1.2	160	133	32	26.6×10^{-12}	0.189	0.[illegible]8	0.1575×10^{-12}	0.1817×10^{-12}	+249.4
7	0.8	60	75	24	30.0×10^{-12}	0.036	0.103	0.0450×10^{-12}	0.1288×10^{-12}	+147.7
Normal aver.	4.9	380	77	138	28.2×10^{-12}	0.210	0.255	0.0428×10^{-12}	0.0520×10^{-12}	

EXPERIMENTAL ANEMIA

To test the results of determinations of blood phosphorus partition in anemic children, experimental anemia was produced in several rabbits and investigations were made in the same manner.

Phenylhydrazine Anemia.—Phenylhydrazine anemia was produced in 2 rabbits by daily injection of 1.2 to 1.5 cc. of 1 per cent phenylhydrazine. The injections were continued until the red cell count was lower than 50 per cent of the normal value. When the experiment started and when the anemia was at its height, blood was withdrawn and analyzed as before. The data concerning the poisoning and the blood count are contained in table 4. In both animals there developed a hypochromic anemia with signs of increased regeneration of the red cells.

The phosphorus partition in whole blood is represented by table 5 and charts 2 and 3.

TABLE 4.—*Blood Counts of Rabbits with Phenylhydrazine Poisoning (Experiments 1 and 2) and Anemia Due to Loss of Blood*

	Date	Red Blood Cells	Hemoglobin, Gm. per 100 Cc.	Hemoglobin, Percentage	Color Index	White Blood Cells	Neutrophils	Lymphocytes	Eosinophils	Monocytes	Basophils	Reticulocytes	Normoblasts
Experiment 1				Phenylhydrazine Poisoning									
Before poisoning.....	11/27/40	5.80	13.3	79.8	0.7	4,750	32	68	0	0	0	0	0
After poisoning *...	12/ 2/40	2.50	5.8	34.8	0.7	11,250	21	76	0	3	0	16	2
	12/ 3/40	3.02	5.8	34.8	0.54	8,000	4	96	0	0	0	18	1
Experiment 2													
Before poisoning.....	12/12/40	4.32	14.2	85.2	0.99	4,500	25	72	0	3	0	0	0
After poisoning †...	12/20/40	1.95	4.0	24.0	0.63	7,800	8	89	0	3	0	16	0
Experiment 3				Anemia Due to Loss of Blood									
Before loss of blood.....	7/23/41	3.21	8.4	50.4	0.79	8,400	75	20	0	5	0	0.8	1
After first loss of blood ‡.....	7/29/41	1.45	4.4	26.4	0.94	.....	..	..	..	..	..	..	..
After second loss of blood §	7/31/41	1.84	5.0	30.0	0.83	3,950	62	28	4	4	2	12.5	3

* On November 28, 1.5 cc. of 1 per cent phenylhydrazine was injected subcutaneously; on November 29, 1.2 cc.; on November 30, 1.6 cc., and on December 2, 0.6 cc.

† On December 14, 1.5 cc. of 1 per cent phenylhydrazine was injected subcutaneously; on December 15, 2.5 cc.; on December 17, 1.8 cc.; on December 18, 2 cc.; on December 19, 1.5 cc., and on December 20, 2.5 cc.

‡ On July 23, 13 cc. of blood was withdrawn; on July 24, 15 cc.; on July 25, 23 cc.; on July 26, 19 cc.; on July 28, 15 cc., and on July 29, 22 cc.

§ On July 30, 23 cc. of blood was withdrawn, and on July 31, 10 cc.

TABLE 5.—*Phosphorus Fractions in the Whole Blood of Rabbits with Phenylhydrazine Anemia (Experiments 1 and 2) and in Blood Loss Anemia (3)*

						Whole Blood							
							Phosphorus (Mg. per 100 Cc.) from						
Experiment	Date	Condition	Red Blood Cells, Millions per Cu. Mm.	Hemoglobin, per Cent	Plasma Inorganic Phosphorus, Mg. per 100 Cc.	Inorganic Phosphorus, Mg. per 100 Cc.	Pyrophosphate	Hexose Phosphates	Glycerophosphate	Acid-Soluble Phosphorus, Mg. per 100 Cc.	Total Phosphorus, Mg. per 100 Cc.	Ratio of Ester Phosphorus to Red Blood Cell Count
1a	11/27/40	Normal.....	5.8	80	5.2	5.3	2.7	7.0	4.5	19.5	24.2	2.5
1b	12/ 3/40	Poisoned.....	2.5	35	5.7	6.0	4.3	9.7	2.2	22.2	33.3	6.5
2a	12/13/40	Normal.....	4.3	80	5.9	6.8	4.6	6.3	22.8	40.5	69.5	7.8
2b	12/21/40	Poisoned.....	1.9	24	4.9	4.6	3.8	8.3	15.6	32.3	72.7	14.6
3a	7/23/41	Before blood loss	3.2	50	4.5	5.9	0.4	5.8	23.9	36.0	64.3	9.4
3b	7/31/41	After blood loss..	1.8	30	...	5.8	1.3	2.9	37.4	47.4	....	23.1

The inorganic phosphorus content was somewhat higher in rabbit 1 and lower in rabbit 2 during anemia, corresponding to the level of inorganic phosphorus in the plasma.

The ester phosphorus in the whole blood of rabbit 1 remained during the anemia at almost the same concentration that it showed prior to the poisoning. In rabbit 2 the anemic blood contained less ester phosphorus than normal blood. The same holds true for the acid-soluble phosphorus

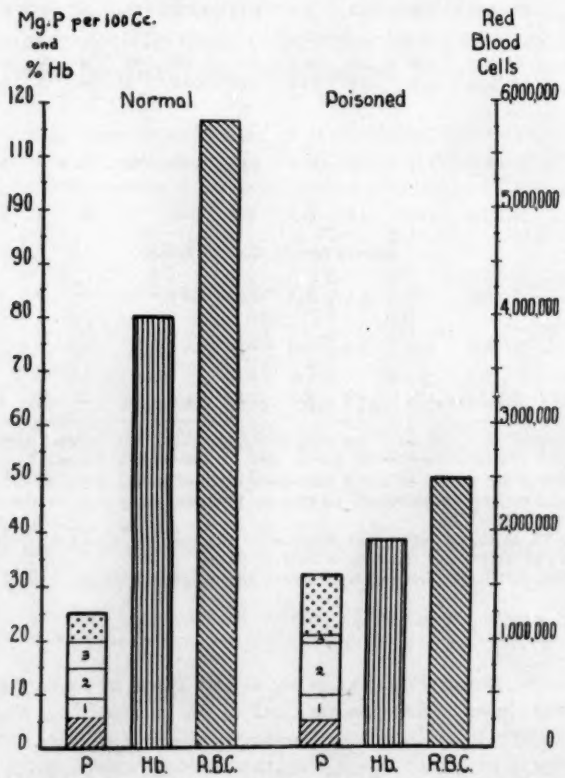

Chart 2.—Phosphorus fractions, hemoglobin and red cells in the whole blood of a rabbit before and during phenylhydrazine poisoning (corresponds to experiment 1 in tables 4 to 7). *Hb*, hemoglobin; *RBC*, red blood cells. Hachure represents inorganic phosphorus; white, ester phosphorus (*1*, from pyrophosphate; *2*, from hexose phosphates; *3*, from glycerophosphate) and dots, lipid phosphorus.

in both rabbits. The changes in the concentration of the different esters were indefinite as far as the whole blood is concerned. Only the glycerophosphate seemed to show a tendency to decrease.

The total phosphorus was increased in the anemic blood of both rabbits. But nothing can be stated from these experiments about the

source of this increase, whether it was from a high content of lipid phosphorus or was due to the presence of nucleic acid phosphorus in connection with the high reticulocyte count.

To summarize, it must be stated that all changes in the different phosphorus fractions in whole blood were small. But this statement is significant in itself for the following reason: When it is recalled that the acid-soluble ester phosphorus is contained only in the erythrocytes, the ester concentration in whole blood must be expected to decrease or

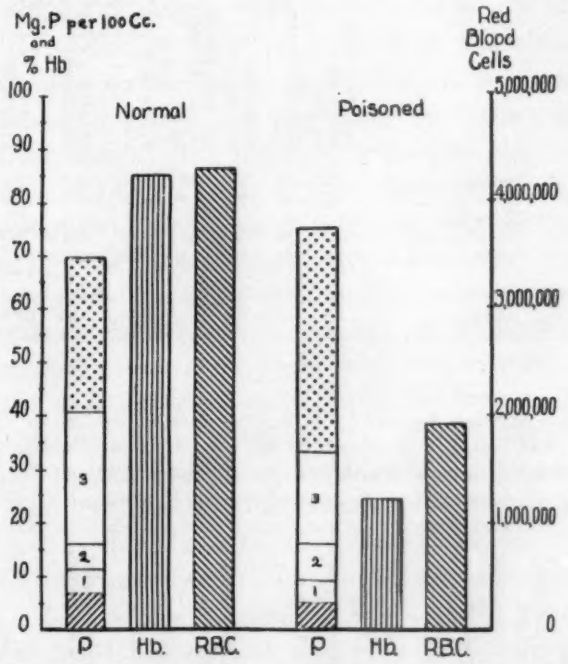

Chart 3.—Phosphorus, hemoglobin and red cells in the whole blood of a rabbit before and during phenylhydrazine poisoning (corresponds to experiment 2 in tables 4 to 7). *Hb* indicates hemoglobin; *RBC*, red blood cells. Hachure represents inorganic phosphorus; white, ester phosphorus (*1*, from pyrophosphate; *2*, from hexose phosphates; *3*, from glycerophosphate), and dots, lipid phosphorus.

increase in correlation with the red blood cell count. One might assume that 2,500,000 erythrocytes carry about half the amount of ester phosphorus held by 5,000,000 red cells. But that is not true. The ester phosphorus concentration in samples of anemic blood remained almost as high as it was in the normal blood, notwithstanding the low red cell count. Therefore, the amounts of ester phosphorus in the erythrocytes were increased. Instead of remaining normal, the ratio of the ester

phosphorus to the red blood cell count rose as a result of the anemia (table 5). In experiment 1 the ratio was increased by 160 per cent (from 2.5 to 6.5 mg. times 10^{-5}); in experiment 2, by 87 per cent (from 7.8 to 14.6 mg. times 10^{-5}).

TABLE 6.—*Phosphorus Fractions in the Erythrocytes of Rabbits with Phenylhydrazine Anemia (Experiments 1 and 2) and with Anemia Due to Loss of Blood (Experiment 3)*

Experiment	Date		Red Blood Cells, Million per Cu. Mm.	Hemoglobin, per Cent	Corpuscular Volume, per Cent	Inorganic Phosphorus, Mg. per 100 Cc.	Phosphorus (Mg. per 100 Cc.) from: Pyrophosphate	Hexose Phosphates	Glycerophosphate	Acid-Soluble Phosphorus, Mg. per 100 Cc.	Ester Phosphorus, Mg. per 100 Cc.
1a	11/27/40	Before.....	5.8	80	34	5.6	7.9	20.6	13.3	47.4	41.8
1b	12/ 3/40	After.....	2.5	35	20	7.2	21.5	48.5	11.0	88.2	81.0
2a	12/13/40	Before.....	4.3	85	32	8.7	14.4	19.7	71.2	114.0	105.3
2b	12/21/40	After.....	1.9	24	18	3.2	21.1	46.1	86.6	157.0	153.8
3a	7/23/41	Before.....	3.2	50	35	8.5	1.4	16.6	68.3	102.9	86.0
3b	7/31/41	After.....	1.8	30	20	...	6.5	14.5	187.0	237.0	208.0

TABLE 7.—*Average Amount by Weight of Hemoglobin, Ester Phosphorus and Acid-Soluble Phosphorus in the Red Cells of Rabbits During Phenylhydrazine Anemia (Experiments 1 and 2) and During Anemia Due to Loss of Blood (Experiment 3)*

Experiment	Red Blood Cells, Millions per Cu. Mm.	Packed Red Cells, Cc. per Liter	Mean Corpuscular Hemoglobin, Cubic Microns	Hemoglobin, Gm. per Liter	Ester Phosphorus, Whole Blood, Gm. per Liter	Acid-Soluble Phosphorus, Whole Blood, Gm. per Liter	Mean Corpuscular Hemoglobin, Gm.	Mean Corpuscular Ester Phosphorus, Gm.	Mean Corpuscular Acid-Soluble Phosphorus, Gm.
1a	5.8	340	59	133	0.142	0.195	23.0×10^{-12}	0.0245×10^{-12}	0.0336×10^{-12}
1b	2.5	200	80	58	0.162	0.222	23.2×10^{-12}	0.0648×10^{-12}	0.0888×10^{-12}
2a	4.3	320	74	142	0.337	0.405	33.0×10^{-12}	0.0784×10^{-12}	0.0942×10^{-12}
2b	1.9	180	95	40	0.277	0.323	21.0×10^{-12}	0.1458×10^{-12}	0.1700×10^{-12}
3a	3.2	350	109	84	0.301	0.360	26.3×10^{-12}	0.0941×10^{-12}	0.1125×10^{-12}
3b	1.8	200	111	50	0.416	0.474	27.8×10^{-12}	0.2311×10^{-12}	0.2633×10^{-12}

The greatly increased amounts of phosphorus carried by the erythrocytes during the experimental anemia are shown in tables 6 and 7. Very significant are the mean corpuscular amounts in the last two columns of table 7. The mean corpuscular acid-soluble phosphorus, for instance,

was increased in the anemic blood by 161.3 per cent in experiment 1 and by 80.4 per cent in experiment 2. Correlation with the mean corpuscular hemoglobin was missing.

Anemia Due to Loss of Blood.—Anemia due to loss of blood was studied in experiment 3. The procedure and the effect on the blood count of the rabbit can be seen from table 4, experiment 3. Blood samples were taken for chemical analysis on July 23, before the bleeding started, and on July 31, when a strong regeneration was in progress and hemoglobin and red cells were increasing again in spite of the daily bleedings. The anemia produced was hypochromic and normocytic.

The phosphorus fractions in whole blood (table 4, experiment 3) showed a tendency to change in a way similar to that in experimental phenylhydrazine anemia. The inorganic phosphorus content was not greatly affected; the organic ester fractions were irregularly changed, but as a whole they showed a higher level than prior to the repeated loss of blood. The acid-soluble phosphorus was increased. Thus the striking feature in the chemistry of this case of anemia due to loss of blood was again the maintenance, or even increase, of the concentration of organic ester phosphorus in the whole blood, in spite of the simultaneous drop of the red cell count and of the hemoglobin content. That could be brought about only by an accumulation of organic esters within the erythrocytes. In tables 6 and 7, experiment 3, this rise of the corpuscular phosphorus fractions is shown. When the experiment started, a moderate anemia was already present and the hemoglobin content was 8.4 Gm. per hundred cubic centimeters of blood; the mean corpuscular ester phosphorus was 0.0941 micromicrogram. Eight days later, when the continued loss of blood had brought the hemoglobin content down to 5.0 Gm., the mean corpuscular ester phosphorus had increased to 0.2311 micromicrogram, i. e. by 145.6 per cent. The corresponding increase of the mean corpuscular acid-soluble phosphorus was 134.9 per cent.

COMMENT

An abnormal concentration of blood phosphorus in cases of anemia may be explained in two different ways. The first possible cause may be the presence in the blood of morphologically abnormal cells, causing an abnormal chemical composition of the blood. Instances are: (1) the simultaneous appearance in the blood stream of considerable amounts of nucleic acid phosphorus and of reticulocytes in the crises of hemolytic

jaundice (Kay[9]); (2) the rise of total lipids, including phospholipids, in erythroblastic anemia (Ericson, Williams, Hummel and Macy[10]); (3) the corresponding increase of white cells and lipid phosphorus in leukemia.[9]

If such a relationship between morphologic and chemical changes in the blood cannot be established, there is another way to explain the abnormal corpuscular concentration of minerals, as suggested first by Farmer and Maizels.[1] As a result of the reduction of hemoglobin in anemic blood, the equilibrium of cations and anions becomes impaired. Hemoglobin is one of the most important base-binding anions in the blood. According to Peters and van Slyke,[11] 8 of 28 milliequivalents per liter of total alkali consists of hemoglobin-bound alkali. To restore the ionic balance the concentration of anions must be raised. Phosphates were found to belong to those anions which can accomplish this compensatory process, which obviously takes place in the erythrocytes. Such a "physicochemical adjustment" may occur irrespective of age and of anatomicopathologic changes of the erythrocytes. It is likely that changes in the concentration of intracellular phosphorus such as those reported in this paper are the result of physicochemical adjustment.

There is no indication that the type of anemia has anything to do with the abnormal distribution of phosphorus. The retention of phosphates was present whether the reticulocyte count was high or low, whether regeneration or destruction prevailed. Neither normoblasts or macrocytes nor a high icteric index (hemolysis) produced a different effect on the phosphorus fractions in the red cells. The 2 cases of hyperchromic anemia did not differ in this regard from the cases of hypochromic or normochromic anemia. Experimental anemia in rabbits showed principally the same chemical picture as anemia in children as far as the phosphorus fractions are concerned.

One may conclude, therefore, that the increase of the ester phosphorus content of the red corpuscles in anemia cannot be ascribed to the anatomic substrate carried by pathologic cells. It would appear more probable that red cells with normal staining properties carry an increased quantity

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9. Kay, E. D.: Blood Phosphorus in Health and Disease: V. Note on the Chemical Composition of the Reticulocyte, Brit. J. Exper. Path. **11**:148, 1930.

10. Ericson, B. N.; Williams, H. H.; Hummel, F. C., and Macy, I. G.: The Lipid and Mineral Distribution in the Serum and Erythrocytes of Normal Children, J. Biol. Chem. **118**:15, 1937.

11. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1.

of phosphorus in anemic conditions as a result of physicochemical adjustment. This conception is supported by the conclusions of Stearns and Warweg,[2] of Farmer and Maizels [1] and of Kinzel.[4]

An analysis of the phosphorus fractions, intracellular and extracellular, in these cases of anemia as well as in Kinzel's, discloses that it is the organic phosphate esters which are responsible for the increased corpuscular phosphorus. It seems that the red blood cell count and the concentration of the intracellular ester phosphorus change in inverse proportion: the lower the cell count the higher the ester fraction. Only once, in the case of extreme leukemic anemia three days before the death of the patient even this regulatory function collapsed. Here the esters were replaced by an enormous amount of inorganic phosphates in the cells.

The retention of phosphorus in the red cells keeps the values of the various phosphorus fractions, as determined in whole blood, in normal or subnormal ranges. The phosphorus partition of the whole blood does not disclose the intracellular retention of ester compounds. Determination of the mean corpuscular phosphorus brings out the changes masked in the values for whole blood.

Studies of Maizels,[12] and of Ericson, Williams, Hummel and Macy [13] and observations by Henrique and Orskow [14] indicate that the concentration of cell cations (potassium, sodium, magnesium) may undergo considerable variations in anemic blood. Further, it must be remembered that the amount of cell water is changed in anemia and that it is difficult to state what part hydration plays in any particular case. This problem must be looked on as still unsolved.

Unsolved also is the question whether microcytic and macrocytic anemia show different variations in corpuscular electrolyte concentration.[10]

SUMMARY

In 7 cases of anemia in children (5 of hypochromic and 2 of hyperchromic type), the phosphorus fractions of the whole blood and of the red cells were determined. The striking feature of the chemical studies was

12. Maizels, M.: The Anion and Cation Contents of Normal and Anemic Bloods, Biochem. J. **30**:821, 1936.

13. Ericson, B. N.; Williams, H. H.; Hummel, F. C.; Lee, P., and Macy, I. G.: The Lipid and Mineral Distribution of the Serum and Erythrocytes in the Hemolytic and Hypochromic Anemias of Childhood, J. Biol. Chem. **118**:569, 1937.

14. Henrique, V., and Orskow, S. L.: Untersuchungen über den Magnesium- und den Kaliumgehalt der roten Blutkörperchen bei Anämie, Scandinav. Arch. f. Physiol. **82**:86, 1939.

an intracellular retention of organic ester phosphorus in 5 cases; in 2 cases the red cells contained the normal amount of phosphorus.

The phosphorus fractions of the blood of 3 rabbits with experimental anemia were computed, with the following results:

In 2 rabbits with phenylhydrazine anemia the corpuscular ester phosphorus was increased; in 1 rabbit with blood loss anemia the corpuscular ester phosphorus was equally increased.

These studies indicate that there is no correlation between the intracellular retention of phosphorus and the presence of any kind of pathologic blood cells or of any special type of anemia.

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INCIDENCE OF PINWORM INFECTION IN WHITE AND IN NEGRO HOSPITALIZED CHILDREN

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Surveys of various population groups in Washington, D. C., by the Division of Zoology, National Institute of Health [1] have shown a lower incidence of pinworm infection in the Negro portion of the population examined than in the white portion. However, comparable groups of the two races were not always available for these earlier studies. The present study was undertaken to determine the incidence of pinworm infection in groups of white and of Negro children held under comparable conditions.

The study was made at Children's Hospital, Washington, D. C., on children hospitalized for medical or surgical conditions, and it is believed to be the first reported investigation of pinworm infection made on hospitalized children. These children were all ward patients, and therefore they represent a low income group.

The subjects were chosen without reference to their medical diagnosis, except that occasionally critically ill patients or patients with infectious diseases were omitted for obvious reasons. During the latter half of the study, only children over 2 years of age were included. This selection was applied to both races.

The NIH swab technic, as described by Hall,[2] was used. The efficacy of this method has been pointed out by Wright and Cram [3] and by Sawitz, Odom and Lincicome [4] after comparison with examinations of the stools of persons known to be infected. The swabs were provided and examined by the Division of Zoology, National Institute of Health.

1. (*a*) Cram, E. B., and Reardon, L.: Studies on Oxyuriasis: XII. Epidemiological Findings in Washington, D. C., Am. J. Hyg. **29**:17-24, 1939. (*b*) Cram, E. B.: Studies on Oxyuriasis: XXIV. Comparative Findings in the White and Negro Races, Proc. Helminth. Soc. Washington **7**:31-35, 1940.

2. Hall, M. C.: Studies on Oxyuriasis: I. Types of Anal Swabs and Scrapers, with a Description of an Improved Type of Swab, Am. J. Trop. Med. **17**:445-453, 1937.

3. Wright, W. H., and Cram, E. B.: Studies on Oxyuriasis: IV. Some Aspects of the Problem of Therapy, Am. J. Dis. Child. **54**:1276-1284 (Dec.) 1937.

4. Sawitz, W.; Odom, V. L., and Lincicome, D. R.: The Diagnosis of Oxyuriasis: Comparative Efficiency of the NIH Swab Examination and Stool Examination by Brine and Zinc Sulfate Flotation for Enterobius Vermicularis Infection, Pub. Health Rep. **54**:1148-1158, 1939.

The swabs were taken by a physician on alternate days between the hours of 11 p. m. and 1 a. m. By the time they were taken, the children had usually been asleep for at least two hours. It was believed that this procedure would allow sufficient time for migration of the larvae to occur and for observations to be made on this phase of the life cycle, about which little is known with regard to hospitalized subjects. However, in spite of the fact that there were 19 egg-containing swabs among those examined, at no time were any migrating worms seen.

Cram and Reardon [1a] have pointed out that at least four swabs, preferably not all on consecutive days, should be made for each child before negative results can be regarded as reliable. In accord with their technic, it was intended to secure at least four swabs from each patient, regardless of results. However, the difficulty in carrying out this plan was soon apparent; it was not a lack of cooperation, as in previous studies, but the mere fact that many of the children were hospitalized for acute illnesses of short duration and were discharged from the hospital before the desired number of swabs could be made. This of course impairs the validity of the negative results obtained, but to the clinician it makes the study of interest, since any investigation in a hospital would present similar difficulties.

Distribution of Pinworm Infection in White and in Negro Children

Negro Children					Number of Swabs from Infected Subjects		First Positive Result			
Age	Sex	Number of Subjects	Total Number of Swabs	Number of Infected Subjects	Positive Result	Negative Result	Swab 1	Swab 2	Swab 3	Swab 4
0-23 mo.	♂	7	24	0	..	..	..	..	..	..
0-23 mo.	♀	8	15	0	..	..	..	..	..	..
2-5 yr.	♂	11	36	0	..	..	..	..	..	..
2-5 yr.	♀	13	35	0	..	..	..	..	..	..
6-12 yr.	♂	12	41	2	2	6	..	..	1	1
6-12 yr.	♀	9	25	0	..	..	..	..	..	..
Total		60	176	2	2	6			1	1
White Children										
0-23 mo.	♂	8	33	1	1	3	..	..	..	1
0-23 mo.	♀	5	12	0	..	..	..	..	..	..
2-5 yr.	♂	15	45	4	4	7	3	..	1	..
2-5 yr.	♀	12	31	4	5	5	2	2	..	..
6-12 yr.	♂	14	41	4	5	3	3	1	..	..
6-12 yr.	♀	6	15	2	2	5	..	..	2	..
Total		60	177	15	17	23	8	3	3	1

For the total series of subjects, the average number of swabs per patient was 2.9. For 96 of the patients, the number was from 2 to 10; only 24 of the series were examined by but a single swab. At least 4 swabs each were taken for 22 of the white and 23 of the Negro children. The summarized results of the examinations are shown in the accompanying table.

Of the 120 children examined, 17, or 14 per cent, were found to be infected. Fifteen of these, or 88 per cent, were white children. Thus there was an incidence of infection of 25 per cent among the white and of 3 per cent among the Negro children. From the accompanying table it is evident that though 28 children under 2 years of age were examined, only 1 infected child was found in this age group. This was an 8 month old white boy. The incidence in white children was the same in the two sexes in the 2 to 5 and 6 to 12 year age groups; the 2 infected Negro children were both boys in the 6 to 12 year age group.

COMMENT

The finding of pinworm eggs in one fourth of the white children may be compared with the results for groups examined by Bozievich [5] and by Cram.[1b] Bozievich reported an incidence of infection of 31 per cent in white boys 6 to 18 years old examined by a single swab from each. An incidence at least as great as his should be expected in the present series, with its larger number of swabs per patient.

Cram [1b] found an incidence of 33 per cent in 209 white children by examining four swabs per patient. This represents a higher incidence for the white group than was found in the present investigation. In the same study, Cram reported 19.8 per cent of the children infected in a series of 131 Negro children examined by four swabs from each. Thus the incidence in Negroes was 60 per cent of that found in white children. The present study, it has been pointed out, shows a much greater variance between the two races.

The present study apparently presents further evidence of lower incidence of pinworm infection in Negro children than in white. It also suggests that hospitalized patients may show a lower incidence than the general population has shown in previous studies. Several factors might be considered of significance in this connection. The effect of fever, of gastrointestinal disturbances, of repeated enemas and of inactivity of the patients might all have some bearing, especially as regards migration of the worms; as previously mentioned, data regarding the time of migration in patients confined to bed are unavailable. Further, these children had rectal temperatures taken four times daily, and the efficiency of the rectal thermometer as a swab is a point to be considered. The thermometers were lubricated with glycerin jelly, and it was noticed when taking the swabs that a small amount of glycerin often remained about the anus. No data were obtained as to the effect of this glycerin on migration of worms or on adherence of eggs to the skin, but its possible effect must also be considered in discussing the low incidence of positive results.

5. Bozievich, J.: Studies on Oxyuriasis: III. The Incidence of Pinworm Infestation in a Group of Two Hundred and Thirty Boys in Washington, D. C., M. Ann. District of Columbia **6**:239-241, 1937.

SUMMARY AND CONCLUSIONS

By means of the NIH swab technic,[2] examinations for pinworms were made on 120 hospitalized children in Washington, D. C., 60 of whom were white and 60 Negro. An incidence of positive results of 14 per cent was found, 88 per cent of the infected subjects being among the white group. Former observations of other workers as to the greater prevalence of pinworm infection in the white than in the Negro population are thus confirmed. Possible effects of hospital environment in determining the low incidence for the series of patients observed are discussed.

Dr. Eloise B. Cram and Dr. Myrna F. Jones, of the Division of Zoology, National Institute of Health, assisted in planning this study and in preparing the report; John P. Folan, of that division, examined the material, and Dr. Joseph S. Wall, of Children's Hospital, Washington, D. C., gave permission to gather and publish this material.

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DIETARY RATIOS FOR THE CHILD WITH DIABETES MELLITUS

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The type of diet with respect to the relative amounts of fat and carbohydrate best suited for patients with diabetes mellitus has been of interest to all investigators in this field of medicine. Before the discovery of insulin, alterations of the diet were practically the only therapeutic approach in the treatment of the disease. Since 1922 there has been a gradual transition toward the use of a more normal diet. There are, however, differences of opinion regarding the type of diet to be employed. Numerous investigators have shown that the relative amounts of fat and carbohydrate influence the response of patients with diabetes mellitus, particularly the patients with uncontrolled diabetes mellitus or with mild diabetes mellitus not receiving insulin. Nelson and Ward reviewed the literature and presented data to show that there is a fairly wide range within which the dietary allowance of children with diabetes mellitus may be varied without the children's losing tolerance, as measured by the amount of insulin required.[1] They stressed the importance of feeding adequate diets. Haist and Best have recently demonstrated the specific effect of the fatty acid: dextrose ratio of the diets on dogs with experimental diabetes.[2] In this clinic emphasis has been placed on diets which are nutritionally complete, and since 1933 a fatty acid: dextrose ratio of 1: 1.5 has been employed.

A study was undertaken to ascertain the practical importance of accurate determination of the fatty acid: dextrose ratio of the diets for children with diabetes. The child with diabetes mellitus practically always requires insulin if he is to ingest and utilize an adequate diet. The major factors known to influence the insulin requirement are severity of the disease, diet, infection, physical activity, emotion and metabolic status. It is possible to standardize the factors of diet and physical activity and to administer insulin to the child with diabetes mellitus who is emotionally stable and free from infection and revert his metab-

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1. Nelson, W. E., and Ward, D.: Diet in the Treatment of Diabetes Mellitus in Children, Am. J. Dis. Child. **55**:487-495 (March) 1938.

2. Haist, R. E., and Best, C. H.: The Prevention of Diabetes, Proc. Am. Diabetes A. **1**:31-48, 1941.

olism to normal. Children with diabetes mellitus will show a typical response to such treatment, and the severity of their disease will become known; that is, the insulin requirement will become constant.[3] Chart 1 illustrates this response to treatment. J. V., a 9½ year old boy, was admitted to the hospital with acidosis and required 106 units of insulin during the first twenty-four hours. Glycosuria was overcome on the

TABLE 1.—*Diet Instructions and Diet Used for J. V., Nine Year old Boy, Whose Response is Shown in Chart 1.*

Diet: P. 98; C. 210; F. 154; Cal. 2,618; D. 283

Breakfast	Gm.
Use each food	
Milk	320
Butter	20
Bread	30
Choose one	
Oatmeal (dry weight)	26
Cornmeal (dry weight)	26
Any other cereal	22
Choose one	
9 per cent fruit	150
Water-packed applesauce	
Water-packed pears	
Water-packed apricots	
Fresh or canned grapefruit	
12 per cent fruit	112
Orange or orange juice	
Pineapple or pineapple juice	
Fresh peach	
15 per cent fruit	90
Fresh apple	
Fresh pear	
6 per cent fruit	225
Honeydew melon	
Canteloup	
Strawberries	
Watermelon	
Dried Fruits	
Prunes	25
Apricots	25
Peaches	22
Raisins	20
Fresh banana	60
Choose one	
Egg	100
Egg	50
and bacon	65
omit butter	10
Ham	70
Cod liver oil (1 tsp.)	4

Dinner	Gm.
Use each food	
Milk	320
Butter	38
Choose one	
Bread	40
Crackers	30
Choose one	
Egg	120
Beef, lamb, veal or canned salmon	80
plus butter	5
Chicken, fresh fish, duck or liver	80
plus butter	10
Dried beef	54
plus butter	12
American cheese	55
minus butter	10
Cottage cheese	80
plus butter	12
minus bread	5
Choose one	
18 per cent vegetable	100
Potato	
Canned kidney beans	
Rice, cooked and thoroughly washed	
Macaroni, cooked and thoroughly washed	
Noodles, cooked and thoroughly washed	
Sweet potato	68
Dried lima beans	26
Banana	80
Bread	35
Choose one	
3 per cent vegetable	100
Tomatoes or tomato juice	
Asparagus	
Cabbage	
String beans	
Spinach	
6 per cent vegetable	50
Beets	
Turnips	
Squash	
9 per cent vegetable	35
Carrots	
Onions	
Peas	
Choose one	
9 per cent fruit	150
Or substitute as listed at breakfast	

Supper	Gm.
Same as dinner	

third day, at which time he received 57 units of insulin. Thereafter the rate of fall was gradual; after twenty-three days the insulin dosage became relatively stable, and by thirty-three days the dose was definitely stable at 22 units.

Only after the insulin requirement has become constant and the daily fluctuation of blood sugar approximates the normal range, should

3. Jackson, R. L.; Boyd, J. D., and Smith, T. E.: Stabilization of the Diabetic Child, Am. J. Dis. Child. **59**:332-341 (Feb.) 1940.

patients with diabetes mellitus be used as subjects for the type of investigation herein reported. In this instance the study period constituted the twenty-five days following the initial observation period.

TABLE 2.—*Changes of Diet* *

Standard Diet [§] Fa:D† Ratio 1:1.5 P. 98; C. 210; F. 154; Cal. 2,618; D. 283	Gm.	High Carbohydrate Fa:D Ratio 1:2.7 P. 104; C. 317; F. 103; Cal. 2,611; D. 387	Gm.	High Fat Fa:D Ratio 1:0.6 P. 90; C. 70; F. 218; Cal. 2,602; D. 144	Gm.
Breakfast		**Breakfast**		**Breakfast**	
Milk	320	Milk	320	Milk	320
Butter	20	Butter	10	Butter	30
Bread	30	Bread	60	Choice of	
Cereal (dry weight)	22	Cereal (dry weight)	22	9 per cent fruit or substitute	50
9 per cent fruit	150	Jelly	15	Egg	100
Egg	100	Sugar	10	Cod liver oil	4
Cod liver oil	4	9 per cent fruit	150		
		Egg	100		
		Cod liver oil	4		
Dinner		**Dinner**		**Dinner**	
Milk	320	Milk	320	Milk	320
Butter	38	Butter	13	Butter or mayonnaise	70
Bread	40	Bread	40	Choice of	
Choice of		Jelly	15	Egg	120
Egg	120	Sugar or stick candy	10	Beef, lamb, veal plus butter	80 5
Beef, lamb, veal plus butter	80 5	Choice of		American cheese minus butter	55 10
American cheese minus butter	55 10	Egg	120	3 per cent vegetable	150
18 per cent vegetable	100	Beef, lamb, veal plus butter	80 5	9 per cent fruit	50
3 per cent vegetable	100	American cheese minus butter	55 10		
9 per cent fruit	150	18 per cent vegetable	150		
30 Gm. of lettuce may be used in addition to the diet		3 per cent vegetable	100		
		9 per cent fruit	200		
Supper Same as dinner		**Supper** Same as dinner		**Supper** Same as dinner	

* This table illustrates the comparison of the changes in diet made during the study period for the 9½ year old boy whose response is shown in chart 1. (This 9½ year old boy's height was that of an average 12 year old, and the diets were figured for the 12 year level. Substi- calories as well as other nutritional factors. The slight caloric difference in fruit and vegetable tutions with the exception of percentage of fruits and vegetables are made on the basis of calories as well as other nutritional factors. The slight caloric difference in fruit and vegetable substitutions is believed to be of no practical clinical significance).

† Fa : D = Fatty acid : dextrose ratio.

TABLE 3.—*Comparison of Average Nutritive Values of Diabetic Diets with Recommended Allowances for Children 10 to 12 Years*

	Calories	Protein, Gm.	Calcium, Gm.	Iron, Mg.	Vitamin A, U.S.P. Units	Thiamine, Mg.	Ascorbic Acid, Mg.	Riboflavin, Mg.	Vitamin D, U.S.P. Units
Recommended allowance	2,500	70	1.2	12	4,500	1.2	75	1.8	600
Diabetic diets (standard)	2,618	98	1.9	13.9	14,052	1.4	118	3.2	600
High carbohydrate	2,611	104	1.9	15.3	13,003	2.2	122	3.2	600
High fat	2,602	90	1.8	10.0	15,349	1.3	72	3.2	600

To stabilize a child with diabetes mellitus requires approximately six weeks of hospitalization with trained personnel. During this period of management the child's state of nutrition approaches a normal level. When the amount of insulin required by the child is known, it is possible to vary experimentally some of the factors previously enumerated and determine the relative significance of each with respect to the requirement of exogenous insulin.

Four children with diabetes mellitus of recent onset were used as subjects after their exogenous insulin requirement under controlled conditions was definitely known, as previously explained. Each child received our standard diet, which is designed to meet all of the known nutritional requirements. The diets were based on a unit formula of protein 7 Gm., carbohydrate, 15 Gm. and fat 11 Gm., with a fatty acid: dextrose ratio of 1:1.5 (table 1). The food was given in three meals,

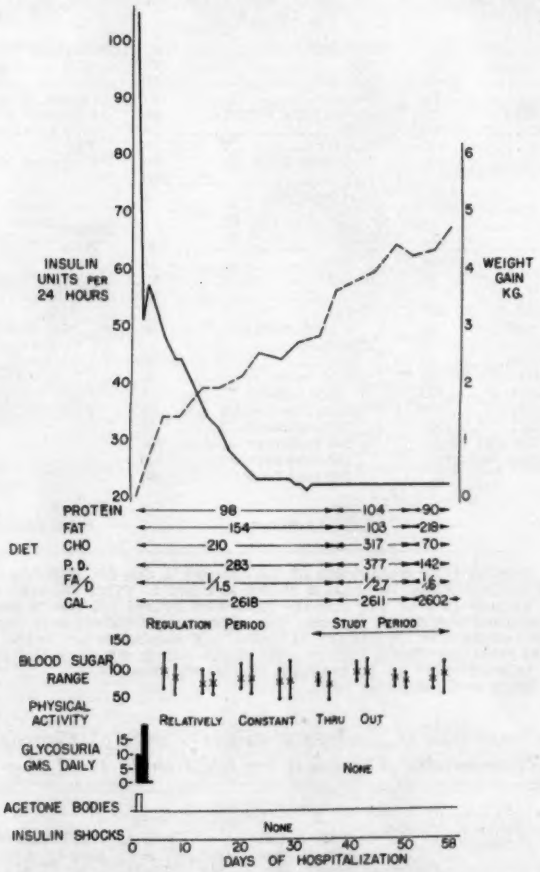

Chart 1.—A record of the response of a 9½ year old boy with diabetes mellitus of recent onset. The heavy line represents daily dosage of insulin; the broken line, gain in weight. The blood sugar values charted represent the mean maximum and minimum and the average values of eight determinations for each day where indicated. Insulin was administered at 6:30 a. m., 11:00 a. m., 4:30 p. m. and once during the night, at 12:00 o'clock. The total day's dose was distributed among the four injections with a percentage distribution of approximately 35, 22, 28 and 15. The fatty acid: dextrose ratio of the diet was shifted after the insulin requirement was constant. The arrows show the demarcation between the period of regulation and the study period. No change in insulin requirement was needed after the change in fatty acid: dextrose ratio; the caloric intake was maintained constant throughout.

each having the same caloric and potential dextrose content and the same fatty acid: dextrose ratio. The children received this diet throughout their period of regulation, at which time their insulin requirement was established. This dietary regimen was continued for a period of approximately two weeks and was then changed for a period of approximately one week of observation to a diet of high carbohydrate content and then for about the same period of time to a diet of high fat content. Each diet had the same caloric value and always remained adequate from the standpoint of known nutritional requirements (tables 2 and 3). Two days a week a series of blood sugar analyses was made for each subject. A micromodification of the Folin-Wu method was used for estimation of sugar content; the Somogyi method of precipitation was

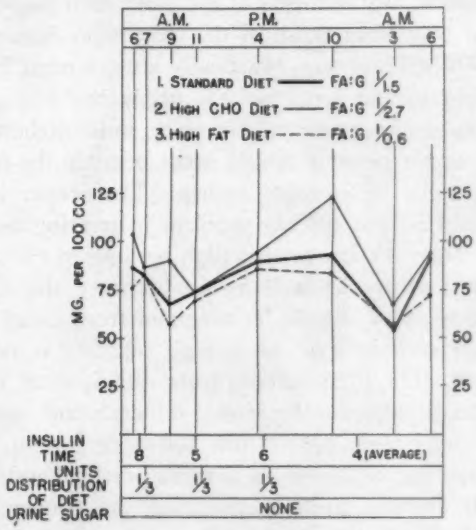

Chart 2.—Average diurnal blood sugar fluctuations of 4 children with well stabilized diabetes mellitus given nutritionally adequate diets of the same caloric content but with varying fatty acid:dextrose ratios, other factors being constant. The children were observed for a total of two hundred and twenty-six hospital days. In each instance the regimen and response had been constant for several days before the blood sugar values were accepted for inclusion (the figures were based on an aggregate of two hundred and fifty determinations of blood sugar made during one hundred and twenty hospital days). The exact data are shown in table 3.

employed. Each subject maintained aglycosuria and freedom from insulin shocks during the period of study.

RESULTS

The results are shown in charts 1 and 2 and table 4. No difference in utilization of any of the three diets was found. The insulin requirement remained constant, and the blood sugar fluctuations approximated

the normal range in each study. The high carbohydrate meals were absorbed more rapidly, resulting in slightly higher postprandial blood sugar values. No child excreted sugar in the urine. While the subjects were receiving the high carbohydrate diet the 10:00 p. m. blood sugar values were slightly higher than the 11:00 a.m. values, and this is probably because the children retired at 7:00 p.m. and hence exercised less after the evening meal than in the morning. The blood sugar values during fasting were always within very close range, implying that the carbohydrate metabolism of these stabilized patients with diabetes mellitus was comparable to that of normal persons.

COMMENT

The basic nutritional requirements of the child with diabetes mellitus should differ in no way from those of the child who does not require exogenous insulin. The child who practically always must have insulin in order to utilize sufficient food for his needs has a problem very different from that of the adult patient with mild diabetes mellitus. Treatment of all younger persons should make possible the maintenance of approximately normal blood sugar values. The proper amount and distribution of insulin is thus the big problem in treating children with diabetes mellitus. Their dietary need is high because of the requirement for growth. Quantitatively as well as qualitatively the diet for the child with diabetes mellitus should be adequate from every nutritional standpoint. A high carbohydrate or a high fat diet is not practical for the child patient. The high carbohydrate diet is most likely to be inadequate from the standpoint of protein, minerals and vitamins, and children with infections often have a low tolerance for fat. A diet as nearly as possible like that of the family is more practical and economical.

The child with diabetes mellitus receiving the proper amount of exogenous insulin with respect to his diet and exercise and who is emotionally stable and free from infection will have normal carbohydrate metabolism insofar as one is able to determine (chart 3).[4] Such a child should be able to utilize food similarly to a normal person. The diets must be quantitative, so as to balance his dosage of exogenous insulin. Our results show that the relative amount of fat and carbohydrate in the diet for a limited period of time makes no apparent difference in the patient's condition. Certainly the exact amount in individual meals would be of no significance. The physician should be concerned to see that the child with diabetes receives a quantitative diet which meets all the known nutritional requirements. The child with diabetes mellitus may be given the same foods prepared for the other members of the

4. Jackson, R. L.; Boyd, J. D., and Smith, T. E.: Interchangeability of Zinc Crystalline Insulin and Amorphous Insulin, Am. J. Dis. Child. **59**:1050-1053 (May) 1940.

TABLE 4.—*Data on Patients Studied*

Patient	Age, Yr.	Sex	Duration in Weeks Before Treatment	Days in Regulation Period	Constant Insulin Requirement, Units	Distribution of Insulin				Study Period FA:D Content of Diet					
						B.	D.	S.	N.	1:1.5		1:2.7		1:0.6	
										Days on Diet	No. of Blood Sugar Determinations	Days on Diet	No. of Blood Sugar Determinations	Days on Diet	No. of Blood Sugar Determinations
G. T.	12	♂	16	14	27	9	6	8	4	21	48	4	16	8	16
J. V.	9½	♂	8	33	22	8	5	6	3	14	32	14	32	8	16
J. F.	12	♂	20	28	33	12	7	9	5	21	16	9	16	5	16
H. S.	14	♀	4	31	13	4	3	4	2	6	16	7	8	3	8
			—	—	—	—	—	—	—	—	—	—	—	—	—
Average			12	26.5	23.75	8.25	5.25	6.75	3.5	15.5	28	8.5	18	6	14

BLOOD SUGAR VALUES FOR EACH STUDY PERIOD

FA:D = 1:1.5

Subject	6	7	9	11	4	10	3	6
G. T.	93	101	67	58	75	93	58	136
	105	87	63	54	76	73	74	107
	87	73	72	79	159	117	59	123
	100	121	69	88	101	101	44	81
	83	76	52	84	85	123	40	79
	86	83	68	49	88	101	39	79
J. V.	83	76	81	72	78	84	76	86
	79	89	60	59	73	91	42	82
	98	76	69	80	90	77	46	52
	55	64	59	82	112	96	44	69
J. F.	93	85	50	63	95	70	46	100
	81	79	44	64	75	127	39	107
H. S.	100	108	79	92	83	92	79	104
	101	71	91	71	71	77	79	85
Average	88	84	66	71	90	94	54	92

FA:D = 1:2.7

Subject	6	7	9	11	4	10	3	6
G. T.	73	83	107	49	119	170	46	96
	91	95	75	88	87	144	57	101
J. V.	97	104	73	75	95	108	76	94
	113	68	98	84	94	118	74	89
	94	80	85	74	78	89	68	75
	80	74	78	76	75	87	63	84
J. F.	127	99	95	76	106	138	67	108
	132	83	100	52	108	151	47	81
H. S.	124	105	111	76	85	107	89	123
Average	103	88	91	71	94	123	65	94

FA:D = 1:0.6

Subject	6	7	9	11	4	10	3	6
G. T.	74	79	35	53	76	73	56	53
	61	59	73	49	80	50	49	77
J. V.	89	77	59	78	89	83	55	89
	100	108	78	74	85	110	52	77
J. F.	60	88	52	59	88	89	50	59
	59	87	36	57	107	112	49	82
H. S.	89	90	72	73	76	83	82	71
Average	76	84	57	63	86	85	56	72

family provided that attention is directed toward making the family's menu correct, but the child must take a definite amount of these foods.

SUMMARY AND CONCLUSIONS

Four children with stabilized diabetes mellitus who were emotionally stable and free from infection maintained approximately normal blood sugar values with a constant insulin dosage and constant amount of physical activity while receiving adequate diets, regardless of the fatty acid : dextrose ratio of those diets. These children with diabetes mellitus, whose disease was treated early and was well stabilized, had a capacity for utilizing food comparable to that of normal persons. It is concluded that in the treatment of the child with stabilized diabetes mellitus emphasis should be directed toward having nutritionally complete diets

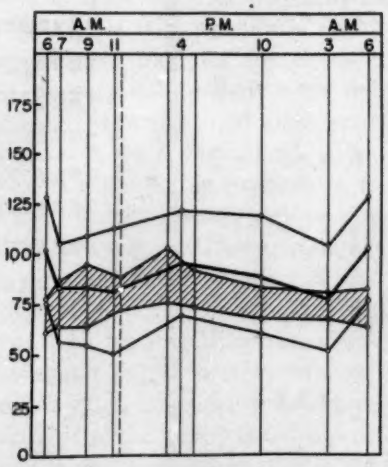

Chart 3.—Diurnal blood sugar fluctuation of normal children as contrasted with that of well stabilized diabetic children. The cross-hatched area represents the gross range of the values obtained for nondiabetic children; the heavy line represents the average values, and the other two curves bound the range included by two standard deviations of the values for children with diabetes mellitus. Each group was under the same dietary regimen; the children with diabetes received insulin. The values show the degree of oscillation and the type of blood sugar level encountered in observations on 31 stabilized subjects. The data, which include an aggregate of nine hundred and six blood sugar estimations made during six hundred and eleven days of study, prove the practicability of maintaining approximately normal blood sugar levels in the diabetic child.

similar to the normal diet and quantitative primarily from the standpoint of calories. If these criteria are satisfied, special attention need not be given the fatty acid : dextrose ratio of the individual meals, and probably not of the entire diet.

University Hospitals.

ISOLATION OF VIRUS FROM A PATIENT WITH FATAL ENCEPHALITIS COMPLICATING MEASLES

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Encephalitic signs accompanying or following the course of measles are among the most frequent nervous complications of the childhood exanthems. There are several theories as to the origin of these disturbances, but none has yet been clearly established as correct. Many clinicians believe that neurotropic properties of measles virus are directly responsible, but there is little or no experimental evidence to support this view or, indeed, any of the following hypotheses. Some consider the manifestations as toxic or allergic responses to the products of the pathogenic activity of measles virus, while others hold that the reactions may be of the anaphylactic type. Certain workers feel that the involvement of the central nervous system may be due to the secondary action of another agent which has been able to invade the body owing to temporary depression of resistance induced by measles virus. Encephalitis complicating measles might thus fall into a group shared with postvaccinal encephalitis and the lethargic type of acute epidemic encephalitis (von Economo's disease). Working along this line, Gay and Holden [1] found that brain material from 3 patients with encephalitis associated with measles failed to produce a reaction on intracerebral injection in rabbits. When inoculated into the skin, however, the brain suspensions did evoke reddening and vesicle formation similar to those observed with material from human or experimental herpes. Furthermore, repeated intradermal injections were found to immunize the animals against intracerebral infection with a herpes strain known to be encephalitogenic for rabbits. There has been no published confirmation of these results.

The isolation of the virus of measles from the central nervous system of a patient with fatal encephalitis complicating measles nine days after

From the Squibb Institute for Medical Research, New Brunswick, N. J., and the Sydenham Hospital, Baltimore.

1. Gay, F. P., and Holden, M.: J. Infect. Dis. **53**:287, 1933.

the rash appeared may have a bearing on this problem of etiology, and the data are therefore presented here.

REPORT OF A CASE

On June 12, 1941, after a fever of several days' duration, R. J., the 7 year old son of intelligent, normal white parents, showed typical Koplik spots and a morbilliform rash developed over his face and neck and spread to his arms, trunk and lower extremities. The child showed no untoward signs until the evening of June 16, when he suddenly began to complain of headache. A few hours later he became unconscious and could not be roused. Later, there were severe generalized convulsions, which persisted throughout the night. The next day the child was brought to the Sydenham Hospital, Baltimore, but he never became conscious during his stay there.

On admission to the hospital, on June 17, he showed a morbilliform maculopapular rash, hemorrhagic in places, over the face, trunk and extremities. Although there seemed no doubt that the child had measles, meningococcic septicemia and Rocky Mountain spotted fever were ruled out by negative results of blood culture and agglutination tests with Proteus OX_2 and OX_{19}. Various therapeutic measures were instituted, among them digitalization, use of sulfadiazine orally and sulfadiazine sodium intravenously and administration of large doses of sedatives, including chloroform, to stop convulsions. He was placed in a respirator on the third day in the hospital, at which time his temperature was 107.6 F. and his respirations were extremely irregular. He was kept in the respirator and seemed to be holding his own until the fifth day in the hospital (June 21), when his pulse suddenly became weak and he died within a few minutes.

At autopsy the only gross macroscopic changes observed in the viscera were in the lungs. The upper lobes of both lungs showed a few dark areas of lobular consolidation, while the lower lobe of the right lung contained a dark solid area in the center, which bulged above the cut surface. In the cranium the cerebrospinal fluid and meninges were not remarkable except for a few small hemorrhages in the latter over both frontal lobes. The venous sinuses contained no thrombi; the blood vessels were normal in appearance, as was the hypophysis. The cranial nerves showed no lesions. The sulci were distinctly flattened, however, suggesting edema of the brain.

Microscopically the lungs showed many areas of lobular pneumonia with cell infiltration of varying sizes and shapes, some of them well circumscribed. The cells were predominantly polymorphonuclear leukocytes, with some mononuclears. On culture the lungs yielded Streptococcus faecalis alpha. The sections of the brain in addition to severe edema in many areas showed small scattered hemorrhages with some accumulation of cells throughout most of the brain substance. There was an infiltration of small mononuclear cells, especially about the small blood vessels, as well as evidence of necrosis in small areas. Many perivascular foci of early demyelination were scattered throughout the brain.

EXPERIMENTAL STUDIES

Inoculations in Small Laboratory Animals.—The autopsy was performed within six hours after death. An attempt was made to remove the brain under aseptic conditions, and portions of the cerebral cortex, medulla and pons were separated. Samples of these tissues were pooled, ground with alundum and made up in a 1:40 dilution in sterile broth. This mixture was centrifuged at 500 revolutions per minute for three minutes and the sediment discarded. The supernatant fluid was cultured aerobically and anaerobically and proved to be sterile with the exception

of two colonies of staphylococci, which grew out on one blood agar plate. Five hundredths of a cubic centimeter of this supernatant fluid was inoculated intracerebrally into each of 3 guinea pigs and 4 hamsters. These animals also received 1 cc. intra-abdominally. Six mice were given 0.03 cc. of the same material intracerebrally and 6 others 0.5 cc. intraperitoneally. Two rabbits were each inoculated intracerebrally with 0.1 cc. and intraperitoneally with 1 cc. None of the inoculated animals showed any signs of disease. They were observed for a period of four weeks and then discarded.

Samples of the pons, medulla and cortex obtained at autopsy were also placed at once in vials, packed in solid carbon dioxide and sent to the Squibb Institute. The material was kept frozen on the "dry ice" for three days and then thawed. The pooled tissues were emulsified in broth to give a 20 per cent suspension, and the supernatant fluid, after centrifugation to remove gross particles, was used for the following experiments.

A sample of the supernatant fluid was diluted with an equal volume of broth and inoculated into animals under ether anesthesia. Three mice each received 0.03 cc. intranasally and 3 mice 0.03 cc. each intracerebrally. A normal guinea pig was inoculated by the following combined routes: 0.15 cc. intradermally and intratesticularly and 0.1 cc. into the pad of a hindfoot. A normal rabbit was inoculated with 0.1 cc. on the scarified cornea, 0.1 cc. intradermally and 0.1 cc. intratesticularly. None of these animals showed any local or general reactions over an observation period of ten weeks, after which they were discarded.

To another portion of the supernatant fluid was added 10 per cent of anesthetic ether by volume. The mixture was shaken frequently by hand over a period of thirty minutes at room temperature. The excess ether was removed by passage of a stream of air, and the suspension was further diluted with an equal volume of broth. With this material also 3 mice were inoculated intranasally and 3 mice intracerebrally. A normal guinea pig received 0.15 cc. intracerebrally and 0.1 cc. intradermally intratesticularly and in the pad of a foot. A normal rabbit was inoculated intracerebrally with 0.15 cc. and intradermally with 0.1 cc. None of these animals showed any local or general reactions over a ten week period of observation.

Egg Transfers.—Embryonated white leghorn eggs of eleven days' incubation were inoculated on the chorioallantois by the Burnet technic with untreated or ether-treated suspension. No lesions were seen on the membranes of either group of eggs after three days' incubation. Serial egg transfers with the untreated material were discontinued because of proliferation of the few staphylococci (Staphylococcus aureus) which had been present in the original suspension. Eleven serial passages on the chorioallantois were carried out with ether-treated suspension before discontinuing. No lesions which could be recognized as characteristic of virus activity were seen, and the emulsions of the membrane did not yield positive cultures when planted on blood agar, in serum broth or in thioglycolate broth. Owing to a shortage of monkeys, egg passage material was not tested by inoculation into these animals.

Inoculations in Monkeys.—Female monkey 2482, weighing 6.7 pounds (3,039 Gm.), was inoculated under ether anesthesia with 10 per cent untreated brain suspension, receiving 1.0 cc. intranasally and 1.5 cc. subcutaneously. Male monkey 2511, weighing 7.7 pounds (3,493 Gm.), was inoculated with ether-treated brain suspension, 0.5 cc. being injected intracerebrally under anesthesia. Both animals (Macaca mulatta) were examined daily according to the technic previously described.[2]

2. Rake, G., and Shaffer, M. F.: J. Immunol. **38**:177, 1940.

Monkey 2482 showed on the fifth day a typical morbilliform maculopapular rash scattered over the chest and abdomen; this cleared by the following day. On the eighth day a lesion closely resembling a Koplik spot was seen on the upper lip, and at this time further typical rash was present, chiefly on the abdomen and to a lesser extent on the face. On the next day the exanthem was already branny, and it subsequently cleared altogether. Leukopenia due to neutrophilopenia was observed from the fourth through the eighth day.

On the fifth day after inoculation, monkey 2511 showed an exanthem of discrete pseudohemorrhagic macules on the chest and abdomen. The rash faded and became branny in the following days, but a recrudescence was noted on the eighteenth and nineteenth days. In this animal leukopenia was not observed, perhaps because of the reaction to the introduction of foreign tissue material into the brain. There was some weakness of the right arm and the right leg together with definite clumsiness persisting until the eighteenth day. Complete recovery ensued thereafter.

Six months later both monkeys and a normal control animal were inoculated with pooled blood taken from 3 human patients with measles in the acute stages. Monkey 2511 showed no signs of measles, while the control animal showed mild but definite disease, with signs of exanthem on the sixth, seventh and twelfth days and of neutrophilopenia from the sixth to the fourteenth day. Monkey 2482 on the ninth day showed a few maculopapules of questionable nature on the abdomen as well as a slight neutrophilopenia.

COMMENT

By the experimental inoculation of animals no virus other than the agent of measles was demonstrated in the brain material from this patient with encephalitis complicating measles. In particular, the application of the material to the skin, cornea, testis, foot pad or brain of animals susceptible to herpes virus by one or more of these routes (namely rabbits, guinea pigs and mice) did not afford evidence for the presence of the latter agent. This was confirmed by the egg inoculations, for it has been found that various strains of herpes virus, whether obtained directly from human sources or from animal passage brains, readily produce typical pock foci on primary introduction on the chorioallantois of the chick embryo.

In both monkeys infected with brain material, albeit by different routes, signs developed which our experience as well as that of others has shown to be characteristic of measles in this species. The disease in animal 2482 was entirely similar to that which we have observed in monkeys after the introduction of human blood or nasopharyngeal washings taken from human patients in the acute stages of measles.

While it is impossible to exclude the presence of some other virus which was not detected by the methods employed, the negative results of our attempts in this direction together with the detection of the virus of measles so long after the onset of the exanthem make it seem probable that the latter agent was responsible for the encephalitis.

It is unfortunate that no blood was taken just before death to be tested for the presence of virus. It is not possible therefore to state dogmatically that the measles virus isolated was present in the substance of the brain and not in the small amount of blood contained in the samples of tissue.

In view of the observation, by other workers as well as ourselves, that measles virus can seldom if ever be recovered from the blood of human beings more than seventy-two hours after the onset of the rash, the isolation of virus in this case so long after the exanthem appeared would be noteworthy, even if the blood should perchance have been the source of the virus.

CONCLUSION

The observation that the measles virus could be recovered from the brain of a patient with fatal encephalitis complicating measles seems of considerable significance, since it not only implicates this agent in the causation of the condition but indicates that the active virus may persist in the human body for as long as nine days after the onset of the rash.

AN ENCEPHALOGRAPHIC RATIO FOR ESTIMATING THE SIZE OF THE CEREBRAL VENTRICLES

FURTHER EXPERIENCE WITH SERIAL OBSERVATIONS

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In a previous communication [1] an encephalographic ratio was proposed for estimating the size of the cerebral ventricles and the degree of atrophy of the brain. The ratio was obtained by dividing the transverse diameter of the anterior horns by the maximum internal diameter of the skull. Measurements were made on encephalographic films exposed in the anteroposterior projection at 30 inches (76 cm.) with the patient horizontal and the occiput down. Considerations of magnification by projection were dealt with and the results in 212 cases reported. In a "normal" group the great majority of the values for the ratio fell between 0.20 and 0.25, and a statistical correlation was obtained between the diameter of the anterior horns and the internal diameter of the skull indicating that the ratio was not influenced by age or by the size of the skull. Values of the ratio between 0.25 and 0.30 were thought to represent borderline enlargement and those above 0.30 a pathologic ventricular dilatation.

It seemed indicated at this point in the investigation to test the effect of some technical factors and common clinical procedures on the measurements used in the ratio and to make serial studies on patients to learn, if possible, the effect of varying quantities of air in the ventricles and other factors on the constancy of the ratio in the same subject.

TECHNICAL FACTORS

The roentgenographic exposure is made ideally with a sagittal ray directed parallel to a line drawn through the outer canthus of the eye and the external auditory meatus and vertical to the film. Owing to the usual difficulties of positioning and restraining the patient, slight degrees of obliquity are commonly obtained. To determine the effect of obliquity on the value of the encephalographic ratio, a group of patients was

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Dr. Alec Klinkowstein collected a large part of the clinical data.

From the Department of Roentgenology of the Children's Hospital of Michigan.

1. Evans, W. A., Jr.: An Encephalographic Ratio for Estimating Ventricular Enlargement and Cerebral Atrophy, Arch. Neurol. & Psychiat. **47**:931-937 (June) 1942.

examined with the skull held in various oblique projections as indicated in table 1. The results indicate that degrees of obliquity greater than those which would be encountered in exercising moderate technical care do not produce important changes in the value of the ratio.

TABLE 1.—*Encephalographic Ratios Obtained from Films Exposed in Various Oblique Projections, Showing Minimal Effect of Slight Degrees of Obliquity in Exposure on Encephalographic Ratio*

Subject *	Initial	Right Oblique	Left Oblique	Chin Up	Chin Down	24 Hr.	48 Hr.	Diagnosis
29	0.65	0.64	0.65	0.64	0.67	0.70	....	Tumor of brain
15	0.41	0.43	0.44	0.40	0.40	0.41	....	Meningococcic meningitis
33	0.62	0.61	0.62	....	....	0.65	0.66	Cortical atrophy convulsions
21	0.33	0.31	0.33	0.33	0.33	....	....	Mental retardation
11	0.36	0.33	0.34	0.34	0.35	0.34	....	Diffuse cortical atrophy

* Numbers based on list in table 4.

TABLE 2.—*Observations Showing Negligible Effect of Intravenous Injection of 50 Cc. of 50 per Cent Sucrose Solution on Encephalographic Measurements*

Subject *	Initial	3 Hours	24 Hours	After Sucrose	Diagnosis
17	0.28	0.28	0.30	0.30	Chorea
21	0.33	0.32	....	0.32	Mental retardation
26	0.36	0.36	0.36	0.36	Mastoiditis, choked disks

* Numbers based on list in table 4.

TABLE 3.—*Measurements Obtained from Flms Exposed Before and After the Removal of Spinal Fluid, Showing Lack of Any Effect of This Procedure on Size of Ventricles*

Subject *	Initial	3 Hours	24 Hours	Fluid Removed	Diagnosis
13	0.265	0.265	0.27	40 cc. —0.28	Dysentery; afebrile convulsions
30	0.27	....	0.29	20 cc. —0.31	Meningococcic meningitis
	(35 days, —0.47; fluid removed, —0.47)				
11	0.36	0.35	....	20 cc. —0.35	Diffuse cortical atrophy
12	0.38	....	0.39	Ventricular tap —0.38	Pneumococcic meningitis
21	0.33	0.32	....	30 cc. —0.32	Mental retardation
35	0.26	0.27	0.28	30 cc. —0.29	Epilepsy

* Numbers based on list in table 4.

For another group of patients (table 2) observations were made before and immediately after the withdrawal of as much spinal fluid as could be obtained. No constant or significant effect was observed in the size of the ventricles on withdrawal of the fluid. This is of interest, inasmuch as the spinal fluid pressure is commonly elevated after encephalography and the postencephalographic headache is commonly relieved by withdrawing spinal fluid.

In a third small group of cases (table 3) no effect could be observed on the size of the ventricles as expressed in the encephalographic ratio on

injection of 50 cc. of a 50 per cent sucrose solution intravenously. Such solutions are sometimes used with the thought of decreasing cerebral edema and lowering intracranial pressure.

TABLE 4.—*Determinations of Encephalographic Ratio Immediately After Injection of Air and at Three Hours, Twenty-Four Hours and Sometimes Longer Intervals*

Subject	Age	Fluid Out/Air In, Cc.	Initial	3 Hours	24 Hours	Other	Diagnosis
1	9 yr.	70/65	0.25	0.26	0.26	.....	Idiopathic epilepsy
2	2 yr.	30/24	0.32	0.33	0.33	.....	Mental retardation
3	20 mo.	?	0.36	0.36	0.37	.....	Diffuse cerebral atrophy; elevated nonprotein nitrogen
4	15 mo.	75/55	0.32	0.31	0.32	.....	Diffuse cerebral atrophy
5	16 mo.	25/20	0.33	0.33	0.33	.....	Diffuse cerebral atrophy
6	6 mo.	53/43	0.34	0.34	0.34	.....	Diffuse cerebral atrophy
7	6 yr.	60/50	0.28	0.28	....	.....	Left jacksonian convulsions
8	11 mo.	45/40	0.30	0.30	0.30	.....	Post-traumatic encephalopathy
9	11 mo.	?	0.29	0.31	0.31	48 hr. 0.30	Frequent convulsions
10	4 yr.	55/45	0.30	0.30	0.30	.....	Epilepsy
11	11 mo.	91/86	0.36	0.35	0.34	.....	Diffuse cerebral atrophy
12	4 mo.	40/15	0.38	....	0.38	.....	Pneumococcic meningitis; died
13	2 yr.	75/65	0.265	0.265	0.28	.....	Dysentery; afebrile convulsions
14	20 mo.	100/80	0.38	0.39	0.40	72 hr. 0.39	Diffuse cerebral atrophy
15	3½ yr.	125/120	0.41	0.41	0.41	72 hr. 0.41	Meningococcic meningitis
16	8 mo.	25/20	0.21	0.21	0.23	.....	Recurrent convulsions
17	9 yr.	90/75	0.28	0.28	0.30	.....	Chorea
18	3 yr.	80/50	0.40	0.41	0.42	.....	Pneumococcic meningitis; died
19	10 yr.	40/32	0.28	....	0.295	.....	Post-traumatic hemiatrophy
20	8 yr.	60/55	0.33	0.33	0.32	.....	Nephritis; occasional convulsions
21	14 yr.	80/75	0.33	0.32	0.32	.....	Mental retardation
22	9 yr.	75/70	0.30	0.29	0.30	72 hr. 0.31	Chronic convulsions
23	9 mo.	80/73	0.34	0.34	....	48 hr. 0.35	Cerebral atrophy
24	2 yr.	55/50	0.30	0.29	0.30	.....	Febrile convulsions (?)
25	10 yr.	75/65	0.26	0.26	0.26	.....	Mental retardation; convulsions
26	8 yr.	.....	0.36	0.36	0.36	72 hr. 0.34	Mastoiditis; choked disks
27	4 mo.	25/20	0.31	0.31	0.33	.....	Mongolism
28	9 yr.	85/75	0.34	0.35	0.37	72 hr. 0.38	Postmastoiditis epilepsy
29	8 yr.	.....	0.65	....	0.70	.....	Tumor of brain; died
30	4 mo.	.....	0.27	....	0.29	.....	Meningococcic meningitis
31	16 mo.	80/55	0.23	0.24	....	.....	Influenzal meningitis
32	6 yr.	75/70	0.27	0.29	0.31	.....	Post-traumatic epilepsy
33	4 yr.	135/95	0.62	0.62	0.65	48 hr. 0.66	Cortical atrophy convulsions
34	3 mo.	32/25	0.44	0.43	0.46	.....	Salmonella meningitis
35	7 yr.	55/35	0.26	0.27	0.28	26 hr. 0.29	Chronic convulsions
36	1 mo.	110/100	0.75	0.74	0.74	.....	Hydrocephalus after meningitis
37	14 mo.	45/47	0.27	0.28	0.31	48 hr. 0.32	Diffuse cerebral atrophy
38	4 mo.	.....	0.28	0.31	0.33	72 hr. 0.39	Cerebral birth injury
39	16 mo.	200/120	0.295	0.30	0.35	48 hr. 0.34	Diffuse cerebral atrophy

SERIAL STUDIES IN A SHORT PERIOD

As is well known, air is rapidly absorbed from the subarachnoid spaces and much more slowly from the ventricles after encephalography. A considerable quantity of air can usually be seen in the lateral ventricles for days and sometimes for a much longer period. This slow absorption of air provides opportunity for observations on the same subject for

two or three days with diminishing quantities of air in the ventricular system. Such observations were carried out when satisfactory measurements were possible for 39 unselected subjects having routine encephalography at the Children's Hospital of Michigan during a period of ten months. Measurements were made on films exposed immediately after the injection of air and after three hours and twenty-four hours. Occasionally, further studies were made at forty-eight or seventy-two hours (table 4).

With a few important exceptions to be examined later, the serial studies at these intervals revealed either no significant change in the size of the anterior horns and the value of the encephalographic ratio or a slight increase. This indicates that the method offers a constant basis

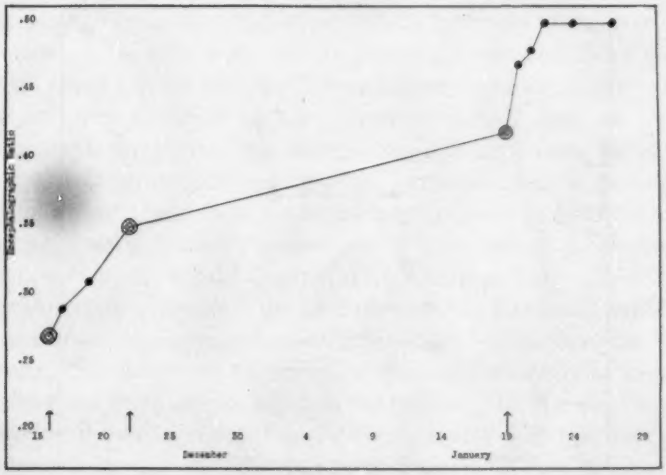

Chart 1.—Serial determinations of the encephalographic ratio in a case of meningococcic meningitis in a 4 month old infant (case 1). The arrows represent new injections of air.

for mensuration within a wide variation in the quantity of air contained in the ventricles and that accurate comparative studies are possible.

A finding of particular interest was the fact that, while a slight enlargement of the ventricles was observed to occur commonly after encephalography, in a few instances a much more striking dilation took place. The first 7 of the 9 cases reported in this paper are illustrative of this. The phenomenon was first forcibly brought to my attention by 2 cases of meningitis (cases 1 and 2), in which with serial observations and repeated injections of air the progressive enlargement of the ventricles could be closely followed. It was apparent from the curves (charts 1 and 2) that not only was there rapid shrinkage of the brain as a result of the inflammatory process, but this seemed to be most pronounced immediately after the encephalographic procedures, as if

aggravated by the presence of air within the ventricles. A similar phenomenon, with changes of a comparable magnitude, was later encountered in an infant suffering from a birth injury to the brain (case 6) and in another infant recently recovered from severe anoxia (case 7). In both of these subjects and in the ones with meningitis, it was evident there had been recent damage to the brain and that a diffuse pathologic process was still active. The mechanism by which the enlargement of the ventricles occurs is not clear. In case 4 the enlargement was not relieved by tapping the ventricles; hence it would not appear that any block or rise in the cerebrospinal fluid pressure in the ventricular system would be a factor. Neither did the withdrawal of a large quantity of spinal fluid in case 7 have any effect in reducing the enlargement. The

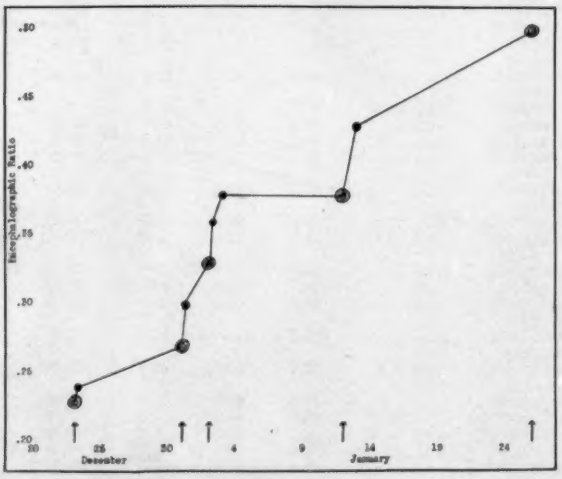

Chart 2.—Serial determinations of the encephalographic ratio in a case of influenzal meningitis in a 16 month old child. The arrows represent new injections of air.

slight apparent decrease in the size of the anterior horns in case 7 was due, I think, to the fact that some of the air was trapped in the temporal horns and there was a critically small amount in the anterior horns. It is readily understandable that when the anterior horns are considerably dilated a larger amount of air is necessary to visualize their maximum transverse diameter and a low critical level in the amount of air will be reached sooner than in a subject with a normal size and contour of the ventricles.

The 3 other cases exhibiting a less striking degree of ventricular dilatation after encephalography were those of a 10 year old boy who had experienced seizures of increasing severity following chronic mastoiditis and a radical mastoidectomy (case 3), a 5 year old boy who exhibited mental defect and spells of headache and vomiting following

a severe injury to the head (case 4) and a 14 month old infant (case 5), who had shown faulty development since shortly after birth. In these cases the evidence for an "active" lesion in the brain is less convincing, particularly as the spinal fluids were all quite normal. However, the close association of the symptoms with the operation which occurred fourteen months before the encephalography and the progressive character of symptoms are presumptive evidence of an active lesion of the brain in case 7, and a similar argument can be made for case 4, in which the injury, accompanied by three days of unconsciousness, occurred one month before the onset of the seizures and seven months before the encephalography.

SERIAL STUDIES OVER A LONG PERIOD

Encephalographic observations after long intervals are apparently not often made. One case from the Children's Hospital of Michigan was reported (case 1) in which some progressive enlargement of the ventricles was noted over a period of four years associated with an aggravation of epileptic symptoms, and another case was cited from the literature of progressive ventricular enlargement accompanying a decline in a patient following a head injury. In contrast to these progressive cerebral lesions, apparently "fixed" lesions are also encountered in which no change occurs in the encephalogram over a long period. Cases 8 and 9 were of this type. In case 8 the first observation was made during convalescence from meningococcic meningitis seven weeks after the onset of symptoms. No change was observed in the encephalographic ratio at the reexaminations three weeks and two years later. At the final study the constancy of the measurements at the three, twenty-four and seventy-two hour observation periods provided further evidence that the lesion was "fixed." The absence of any deterioration in the patient's mental status would also support this view. Case 9 was an instance of injury to the brain associated with an extensive fracture of the skull. Although there was evidence of diffuse damage in the brain, this was particularly severe in the right occipital area, as shown by blindness and the particular enlargement of the posterior horn of the right lateral ventricle. Encephalographic studies with intraspinal injections of air were made at four weeks and eight months after the injury. Not only was there no change in the encephalographic ratio during this interval, but there was no change at the three and twenty-four hour observation periods, which gave further evidence of the fixed character of the lesion in the brain after recovery from the acute symptoms.

CONCLUSIONS

Serial determinations of the encephalographic ratio indicate a constant basis for mensuration, even with great variations in the amount of air.

The roentgen exposure should be made in the anteroposterior projection in the sagittal plane with the ray vertical and with the head held with the occiput down, so that a vertical line will pass through the outer canthus of the eye and the external auditory meatus. Moderate degrees of obliquity of the skull in the sagittal and coronal planes produce no significant or constant changes in the measurements.

Many subjects show no change in the measurements at the three and twenty-four hour periods, but in the majority there is a tendency for the ventricles to increase slightly in size in the presence of air.

The dilatation is not reduced by spinal tap or influenced by the intravenous injection of hypertonic solutions.

The dilatation is much more pronounced in the presence of an active diffuse cerebral lesion, in which case a rapid and irreversible dilatation of the ventricles may occur.

It is recommended that serial measurements be made for forty-eight or seventy-two hours in pneumoencephalography. If no change in the measurements occurs, the presumption is that any diffuse cerebral lesion which may be present is "fixed." If the ventricles enlarge, there is presumptive evidence that the lesion is active and progressive. The rate of enlargement seems to be proportional to the degree of "softening" of the brain.

REPORT OF CASES

CASE 1.—P. S. (subject 30, table 4), a white girl, was born by a normal delivery on Aug. 7, 1941 and was admitted to the Children's Hospital of Michigan on December 6, with a history of having been fretful and feverish for one week, with some vomiting and stiffness of the neck and spine later. A spinal puncture disclosed 1,240 white cells in the spinal fluid, with 69 per cent of the cells polymorphonuclear leukocytes, and meningococci were identified on smear and by culture. Treatment was the administration of sulfadiazine, first intravenously (as sodium sulfadiazine) and then by mouth, for a period of fifty-seven days. On the seventh day after the patient's admission 20 cc. of antimeningococcus serum was given intravenously and on the following day 10 cc. intraspinally with air. Repeated examinations of the spinal fluid showed a few hundred white cells per cubic millimeter, and at the last tap, on Jan. 20, 1942, there were 180.

She was readmitted on February 25, with otitis media on the left side, and at that time the spinal fluid appeared normal.

Encephalographic studies were carried out on Dec. 16 and 22, 1941 and on Jan. 19, 1942, with repeated measurements of the encephalographic ratio, as indicated in the chart (chart 1).

CASE 2.—T. O'B. (subject 31, table 4), a white boy, was born on July 20, 1940 with the aid of instruments after a labor of seventeen and one-half hours. He cried immediately. On Dec. 16, 1941, after an illness with fever and vomiting for two days, he was admitted to the Children's Hospital with convulsions. The spinal fluid contained 7,120 white cells per cubic millimeter, and the influenza bacillus was obtained by culture. Treatment was sedation by means of soluble phenobarbital U. S. P. (sodium phenobarbital) for the convulsions and injection of sodium sulfadiazine and anti-influenzal horse serum intravenously and intramuscularly for the infection. Cultures of the spinal fluid did not yield influenza

bacilli after the second day; the cell count dropped to a low level after one week, and the fever disappeared in about four weeks. A temporary recurrence of fever was noted on Feb. 3, 1942 associated with a bilateral otitis. Discharge from the hospital occurred on February 13, with the patient showing signs of extreme mental retardation, being unable to hold up his head and having poorly coordinated movements.

Encephalographic studies were carried out on five occasions, and the values of the encephalographic ratio are recorded in chart 2.

CASE 3.—A. O. (subject 28, table 4), a white boy born by a normal full term delivery on Aug. 20, 1932, had a Rammstedt operation for pyloric stenosis at the age of 3 weeks, from which recovery was uneventful. In 1937 he suffered an attack of scarlet fever followed by mastoiditis and mastoidectomy on the left side. A discharging fistula persisted in spite of local applications and a tonsillectomy in 1939, and finally a radical mastoidectomy was carried out on July 8, 1940, during which a number of dural exposures were made.

There seemed to be satisfactory healing of the local wound, but after the operation the patient experienced spells of twitching, nausea and pallor lasting one or two minutes. These increased in frequency during the two weeks prior to admission to the hospital on Sept. 22, 1941, and on the day of admission there were three convulsions with loss of consciousness. Five days later a spinal puncture yielded normal fluid, and an encephalogram was made on September 29 with removal of 85 cc. of spinal fluid and injection of 75 cc. of air. Measurements obtained from the films exposed in the anteroposterior projection were as follows:

	Transverse Diameter, Cm.		
	Anterior Horns	Skull	Ratio
9/29/41	5.4	15.7	0.34
3 hr.	5.6	15.8	0.35
9/30/41	5.9	15.8	0.37
10/ 2/41	6.0	15.8	0.38

The lateral ventricles were enlarged about equally, and there was no displacement or deformity in the ventricular system, except that at twenty-four hours there seemed to be some displacement of the interventricular septum toward the right. On September 30 a spinal tap yielded 4.5 cc. of clear fluid, containing 240 cells, one half of which were erythrocytes.

CASE 4.—D. McC. (subject 32, table 4), a white boy born by an apparently normal full term delivery on June 24, 1936, sustained an injury to the head in a fall of 14 feet (4.25 meters) in June 1941 and was unconscious for three days. Beginning about a month later there were spells of vomiting and headache. Nothing of a focal nature was noted. His school work was poor, and he showed a faulty memory and poor coordination at times. The physical examination disclosed nothing of diagnostic interest. The tuberculin and Kline reactions were negative.

On Feb. 26, 1942 encephalography was performed with the injection of 75 cc. of air, and the following measurements were obtained:

	Transverse Diameter, Cm.		
	Anterior Horns	Skull	Ratio
2/26/42	4.6	17.1	0.27
3 hr.	4.9	17.0	0.29
2/27/42	5.2	17.0	0.31

CASE 5.—J. D. (subject 37, table 4), a 14 month old white boy, a private patient of Dr. T. B. Cooley, was said to have been born by normal delivery three weeks after the expected termination of pregnancy. He had nursed well for six months but had difficulty with solid foods. Backwardness was noted at

8 months. He made no effort to sit erect and slept a great deal, not attempting to cry or to form words. There was no history of infection.

The physical examination disclosed a small head and the general appearance of idiocy. There was a pronounced lack of tone in the muscles of the back and neck, causing the head and trunk to bend forward. No change in the reflexes from the normal was observed, and there was no spasticity or other alteration in the tone of the muscles of the extremities.

The encephalogram made on June 1, 1942, with removal of 45 cc. of spinal fluid and injection of 27 cc. of air, disclosed a symmetric dilatation of the lateral ventricles without displacement or pressure deformity. The following measurements were obtained:

	Transverse Diameter, Cm.		
	Anterior Horns	Skull	Ratio
6/1/42	3.3	12.0	0.275
3 hr.	3.4	12.0	0.28
6/2/42	3.8	12.1	0.315
6/3/42	3.9	12.0	0.325
15 cc. of spinal fluid removed and 10 cc. of air injected			
6/3/42	3.9	12.1	0.32

Case 6.—J. T. (subject 38, table 4), a white boy, was born at term on Feb. 14, 1942, weighing 7 pounds 4½ ounces (3,303 Gm.). The delivery was prolonged and difficult, finally being accomplished by rotation, with use of a forceps, and then version, with a breech extraction. Prolonged resuscitation was required, and fractures were sustained in the left humerus and left clavicle. Spasticity was noted in the extremities of the left side, followed by flaccid paralysis. Two days after birth many furuncles appeared on the scalp, and later there were abscesses in the left buttock and knee, from which sterile pus was obtained. Culture of the blood gave negative results. Sulfapyridine was given daily.

On May 27 the child was readmitted to the Children's Hospital following a convulsion which had lasted one hour, with twitchings of the left arm and leg. He was comatose, and there was a lead pipe rigidity of the extremities with the reflexes hyperactive. A subdural tap performed (June 25) on the left yielded no fluid, but on the right some xanthochromic fluid was obtained. A spinal tap (May 29) yielded fluid contaminated by blood, and at a ventricular tap (May 30) clear fluid was obtained on the left and bloody fluid on the right. On June 7 there were generalized convulsions, and 20 cc. of xanthochromic fluid was removed from the subdural space. An osteoplastic flap was turned down in the right parietal area on June 10, but subdural pathologic conditions were not found. All fluids obtained were sterile on culture. Encephalographic studies were carried out on June 26 and the serial observations following this single injection of air reveal a rapid increase in the size of the lateral ventricles.

	Transverse Diameter, Cm.		
	Anterior Horns	Skull	Ratio
6/26/42	3.9	13.7	0.28
3 hr.	4.3	13.8	0.31
6/27/42	4.6	13.8	0.33
6/29/42	5.3	13.7	0.39
30 cc. of xanthochromic subarachnoid fluid removed over left cerebral hemisphere and 15 cc. of clear fluid over right			
6/29/42	6.0	13.6	0.44
7/ 6/42	100 cc. of subarachnoid and ventricular fluid removed on the right and 90 cc. of air injected		
	5.7	13.8	0.41
7/10/42	120 cc. of fluid removed from right side of skull and 40 cc. from left; 100 cc. of air injected on the right		
	5.7	13.7	0.42

CASE 7.—G. S. (subject 39, table 4), a white boy born on Feb. 22, 1941, had always seemed retarded in his development. He could not sit up without aid but would remain sitting up if placed in that position. He could speak a few words, however, and seemed to understand when spoken to. On June 17, 1942 he fell forward in a play car with his neck pressing against a wire. He was found deeply cyanotic and unconscious, and respirations had ceased. After two hours of artificial respiration and the administration of epinephrine and caffeine, he was revived. He then had a convulsion and was admitted to the hospital on the following day. Reactions to tuberculin and Kline tests were negative. Spinal fluid examinations on June 18, July 1 and July 10 revealed no abnormality. Encephalographic studies were carried out on July 1 and July 10 with the injection of 200 cc. and 120 cc. of air on these dates, respectively.

Measurements obtained from the films exposed in the anteroposterior projection were as follows:

	Transverse Diameter, Cm.		
	Anterior Horns	Skull	Ratio
7/ 1/42	4.55	15.5	0.295
3 hr.	4.75	15.7	0.30
7/ 2/42	5.50	15.7	0.35
7/ 3/42	5.35	15.7	0.34
7/ 4/42	5.3	15.7	0.34
7/ 6/42	5.05	15.6	0.32
7/ 7/42	5.6	15.7	0.36
7/ 8/42	5.6	15.5	0.36
7/10/42 200 cc. of spinal fluid removed and 120 cc. of air injected			
	6.4	15.4	0.42

CASE 8.—L. W. (subject 15, table 4), a white girl born by a normal delivery on Sept. 20, 1938, was first seen at the Children's Hospital on March 23, 1940 with meningococcic meningitis, with a duration of symptoms of six weeks. Recovery occurred following the administration of sulfapyridine intravenously (as sulfapyridine sodium) and by mouth. Encephalographic studies were carried out on March 30, when the spinal fluid still had a high protein content and contained 610 white cells per cubic millimeter, although it was sterile on culture. There was a slow, uneventful convalescence, with a gradual fall in the protein and the cellular content of the spinal fluid. Spinal fluid removed at an encephalographic study on May 21 showed no globulin and only 10 white cells.

She was readmitted to the hospital on Jan. 29, 1942, about two years after the onset of the meningitis, with an acute bronchopneumonia following pertussis. Recovery was rapid. In view of the hydrocephalus previously observed, psychometric studies were carried out by means of Merrill-Palmer tests. The developmental patterns were regarded as somewhat unusual but nevertheless indicative of the average mental state for the patient's age. An encephalogram was made at this time (February 6), with removal of 125 cc. of spinal fluid and injection of 120 cc. of air. The fluid contained 610 white cells, with 80 per cent polymorphonuclears, and no organisms were demonstrated on smear. The following measurements were obtained from the encephalograms:

	Transverse Diameter, Cm.		
	Anterior Horns	Skull	Ratio
3/30/40	5.4	12.9	0.42
5/21/40	5.5	13.7	0.40
2/ 6/42	6.0	14.8	0.41
3 hr.	6.1	14.9	0.41
2/ 7/42	6.1	14.8	0.41
2/ 9/42	6.1	14.9	0.41

CASE 9.—A. R. (subject 8, table 4), a Negro girl, was born on Nov. 22, 1940. On Sept. 21, 1941 she fell from a second story window and was admitted uncon-

scious to the Children's Hospital. A gaping linear fracture was demonstrated in the parietal and occipital bones on the right side. Soon after consciousness returned, the patient was observed to be blind. The optic disks appeared normal. Encephalographic studies were carried out on October 24, with removal of 40 cc. of normal spinal fluid and injection of 35 cc. of air. The ventricles were observed to be dilated, especially in the right posterior horn, and there was enlargement of the sulci.

She entered the hospital again on May 4, 1942 after another fall, with injury to the occiput. She became dazed about three quarters of an hour after the injury and would not respond to questions. Later there were convulsive movements of the left hand and arm. The spinal fluid was found to be normal. No new fracture was demonstrated, and recovery was rapid. An encephalogram was made on May 11, with removal of 30 cc. of fluid and injection of 20 cc. of air. The ventricles were incompletely visualized, and on May 13 35 cc. of fluid was removed and 30 cc. of air injected.

The following measurements were obtained from the encephalographic films:

	Transverse Diameter, Cm.		
	Anterior Horns	Skull	Ratio
10/24/41	4.2	13.9	0.30
3 hr.	4.15	13.8	0.30
10/25/41	4.2	13.8	0.30
5/11/42	4.05	14.3	0.28
3 hr.	4.05	14.2	0.29
5/13/42	4.1	14.2	0.29
3 hr.	4.15	14.2	0.29
5/14/42	4.2	14.2	0.30

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OSTEOCHONDROSIS DEFORMANS TIBIAE

NONRACHITIC BOW LEG IN CHILDREN

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Osteochondrosis of the medial tibial condyle is at the time of writing the most common cause of development of bow leg during childhood in this community. That this condition has not been more widely recognized is undoubtedly on account of the diversity of names by which it has been designated in previous reports. Since Blount [1] called attention to it as a cause of acute bending of the legs in children, I have encountered no less than a dozen cases in which the deformity might rightfully be attributed to osteochondrotic changes in the tibial epiphyses. Although the children had received adequate amounts of vitamin D and although other evidence of rickets was wanting, the parents either had been told or were of the opinion that the deformities of the legs were due to that disease. To have been told or to have believed otherwise would not have been in accord with former teaching.

The changes observed in osteochondrosis of the medial tibial condyle are definite and need not be confused with those seen in rickets, whether due to deficiency of vitamin D or of the renal or the colonic variety, nor should they be confused with the deformities which may accompany dyschondroplasia (Ollier's disease), achondroplasia, fragilitas ossium or osteogenesis imperfecta.

The roentgenographic and pathologic changes are like those of coxa plana and those in the many bones similarly involved elsewhere but are quite different from those of rickets. When the tibial condyles are involved, two distinct types occur. These two types are dependent on the age at which the condition becomes manifest, and they have been designated as the infantile and adolescent types of the disease denominated by the less cumbersome though more grossly descriptive term "tibia vara".[1]

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Read before the Section on Orthopedic Surgery at the Ninety-Third Annual Session of the American Medical Association, Atlantic City, N. J., June 10, 1942.

1. Blount, W. R.: Tibia Vara: Osteochondrosis Deformans Tibiae, J. Bone & Joint Surg. **19**:1-29, 1937.

THE INFANTILE TYPE

In cases of infantile type (fig. 1) a history of normal development, except for some overweight for one or two years, is usually obtained. The deformity usually occurs bilaterally and when mild may disappear on one or both sides spontaneously. When it is unilateral there is a limp in walking, and when it is bilateral, there is a waddle. The bowing is evident as an abrupt angulation with the apex laterally just below the knee. In fat children this angulation appears to be a gradual curve. When the deformity occurs during infancy, a bulbous enlargement of

Fig. 1.—(*A*) W. R., aged 17 months. (*B*) Roentgenogram of W. R. (from Barber [2]).

the medial tibial condyle is palpable on physical examination and visible in the roentgenogram (fig. 2). This beaklike projection at the metaphysis has been shown to contain islands of cartilage (fig. 3).[1] Recurvation of the knee and relative flatfoot are present, irrespective of the age. Abnormal mobility of the knee on medial strain with normal stability on lateral strain and inward rotation of the tibia on the femur are common. A general medical examination usually reveals no other abnormalities. There is nothing suggestive of rickets or syphilis.

Faulty growth of the upper tibial epiphysial cartilage and delayed ossification of its medial half result in a wedge-shaped deformity of the

epiphysis. The lower tibial epiphysial cartilage occasionally shows similar though less pronounced changes (fig. 1*B*); if this occurs, some lateral bowing just above the ankle may appear.[2] Elsewhere the tibial

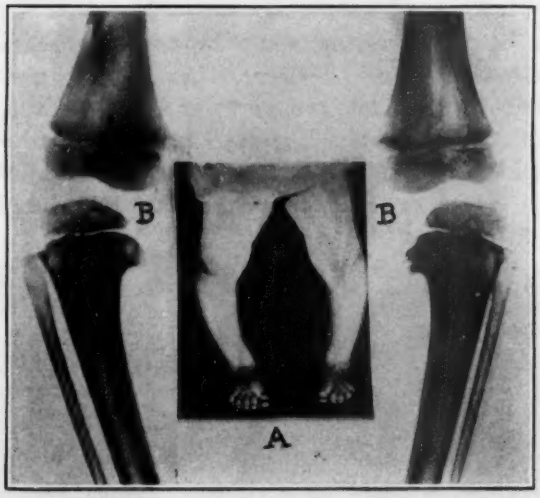

Fig. 2.—(*A*) J. H., aged 3½ years. (*B*) Roentgenogram of J. H. (from Blount [1]).

Fig. 3.—Tracing from a roentgenogram showing cartilage restored in a child aged 3½ years: *A*, angulated shaft; *B*, widened epiphysial line; *C*, wedge-shaped epiphysis; *D*, beaklike metaphysis; *E*, cartilage islands. (Redrawn from Blount.[1])

2. Barber, C. G.: Osteochondrosis Deformans Tibiae, Am. J. Roentgenol. **42**:498-502, 1939.

shaft is perfectly straight. Secondary changes in the medial femoral condyle may augment the deformity.

THE ADOLESCENT TYPE

The onset of the adolescent type is between the ages of 6 and 12 years in previously normal children. The deformity usually occurs on one side only. The adolescent type looks different in the roentgenogram (fig. 4*A*). It is an arrest of growth rather than a dysplasia. The roentgenographic appearance of the infantile type gradually changes to that of the adolescent type, so that the two can be distinguished later only by the history.

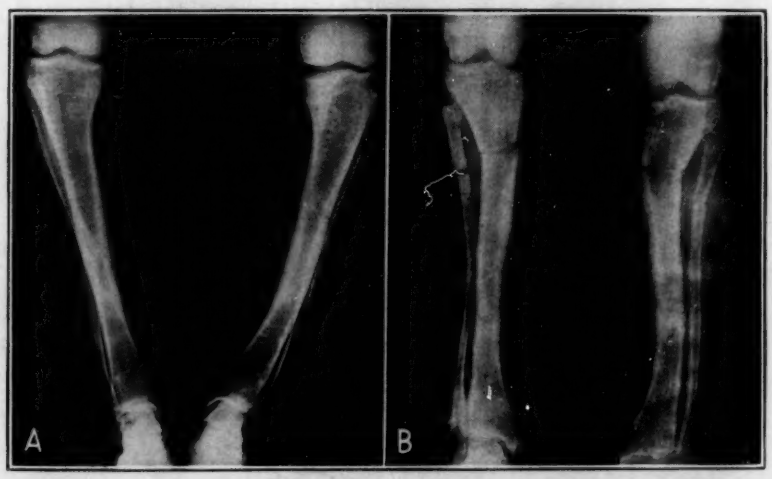

Fig. 4.—(*A*) Roentgenogram of the legs of H. C., aged 17 years, taken before the final operation. (Bowing recurred after two previous operations.) (*B*) Roentgenogram taken after the final operation, showing the correction obtained by operation.[2]

TREATMENT

Since spontaneous recovery on one or both sides sometimes does occur with the milder forms of the infantile type [1] and since recurrence (fig. 4) has been experienced by various operators when surgical correction was resorted to before the condition had become arrested,[3] attempts to prevent further deformity or even to correct the existing deformity by nonsurgical means seemed justifiable.

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3. Lewin, P.: Epiphyses: Their Growth, Development, Injuries and Diseases, Am. J. Dis. Child. **37**:141-178 (Jan.) 1929. Lülsdorf, F.: Epiphysitis tibiae deformans, Ztschr. f. orthop. chir. **53**:64 and 162, 1931. Rall, G.: Genua vara wegen Deformierung der Tibiaepiphysen, ibid. **61**:202-205, 1934. Rocher, H. L., and Roudil, G.: Genu varum droit ostéogénique par hématrophie congénitale de l'épiphyse tibiale supérieure, Acta chir. Scandinav. **66**:275-292, 1930.

It was found that correction of the milder forms could be effected by daily manipulation of the legs by the parents and the use of a wide elastic bandage which encircled the legs to exert a corrective force when the child slept. To ease the force of the elastic band and to hold the legs in a position favorable to correction, a pair of the child's shoes fastened together with a piece of crepe rubber or heavy felt interposed were worn at night. The results obtained through such simple means in the treatment of patients with mild deformity suggested added effort in an attempt to straighten the legs by continued force even though the bowing was extreme.

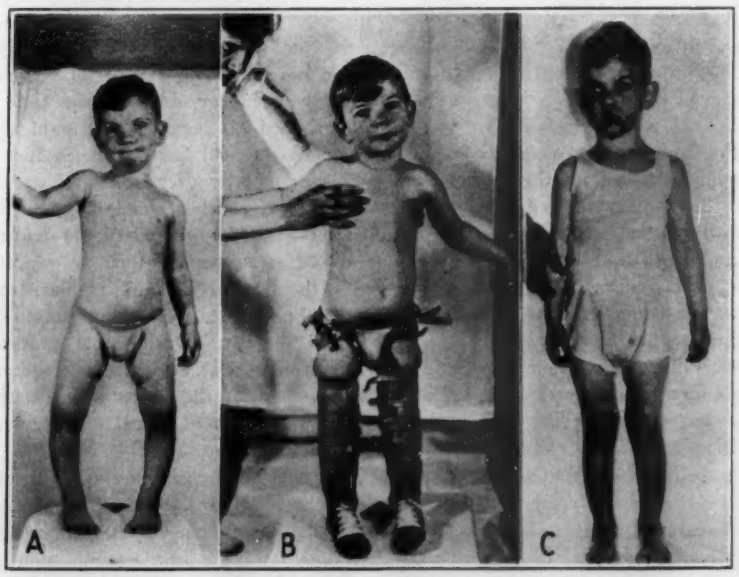

Fig. 5.—J. S., aged 2 years. *A* shows the deformity before correction was commenced; *B*, corrective braces applied; *C*, the degree of correction obtained.

REPORT OF CASES

CASE 1.—J. S. (fig. 5 *A*), a white boy aged 2 years, was first seen in June 1938 because of gradually increasing bow leg. He began to walk at the age of 1 year, at which time, the parents claimed, his legs were not bowed. Five months later they noticed some bowing, but during the subsequent ten months the deformity had increased greatly.

He was breast fed for thirteen months, and his diet was supplemented with vegetables at 10 months. He had been given orange and tomato juices regularly almost from birth, and during the winter months he had received plenty of cod liver oil.

When first seen he walked with a decided waddle, and both legs were badly bowed. The bowing was almost entirely adjacent to the knees and was accompanied by some recurvation and internal rotation of the lower parts of the legs.

There was abnormal mobility on medial strain with normal stability on lateral strain. A bulbous projection could be felt in the medial part of each upper tibial metaphysis.

The roentgenograms revealed a mild osteochondrosis, with the characteristic sloping of the medial half of each upper tibial epiphysis.

Braces (fig. 5 *B*) with an inside upright by which corrective force could be continuously applied, aided by daily manual manipulation, converted a moderate bowing of the legs to a mild degree of knock knee (fig. 5 *C*) within a four month period. The relative flatfoot and the inward rotation of the legs disappeared simultaneously with the correction of the bowing. Twice during this period treatments were interrupted because of infections of the upper respiratory tract.

He continues to wear his braces at night but not during the day.

CASE 2.—T. G. (fig. 6 *A*), a white boy, aged 5 years when first seen in August 1940, presented an extreme bowing of his legs, which caused him to waddle awkwardly on walking. He had been breast fed for one year and had received cod liver oil intermittently thereafter. He had never been ill except for an occasional cold. He began walking when he was about 1 year old, at which time he weighed 21 pounds (9.5 Kg.). His parents claimed his legs were straight until he was 2 years old, when the repair of a right inguinal hernia caused him to be confined to bed for three weeks. A couple of months after he began walking again, the mother noticed some bowing of his legs, which seemed to be getting gradually worse. At that time the parents were advised to disregard the deformities and were told that their child's legs would straighten of their own accord as he grew older. They were dissatisfied with such advice, and regular treatments, consisting of exposures to sun rays and massage, were administered for an entire year by a practitioner of mechanical therapy. During that year and the one following, a gradual increase in the deformities was evident. The succeeding six months, however, witnessed an unusual increase in the degree of angulation. Somewhat perturbed, the parents sought other counsel, and when told the boy's condition was due to rickets, they were justly resentful.

On examination the bowing of T. G.'s legs, although extreme (the distance between the medial condyles measured 7½ inches [19 cm.] during recumbency), was mostly adjacent to the knees, the legs elsewhere being relatively straight. There were no other signs of rickets. The knees were most unstable on medial strain but stable on lateral strain. On standing he presented in addition to the lateral bowing a decided recurvation, inward rotation of the lower legs and relatively flat feet. A large beaklike projection was palpable on the medial side of each upper tibial metaphysis. The roentgenogram (fig. 6 *D*) revealed changes, although extreme, which characterize the accompanying structural derangement in osteochondrosis of the upper tibial epiphyses.

Although it seemed illogical to expect complete correction of such extreme deformity without resort to surgical intervention, it seemed logical to assume from the existing evidence that the conditions permitting the deformity to develop had not yet become stabilized. Since recurrence of the deformity could be expected if surgical correction were resorted to before arrest of the condition was assured, measures were instituted to prevent further deformity and in so far as possible to correct the existing deformity. Therefore, on November 4 the patient was confined to bed, with standing and walking disallowed. On November 19, physical therapy in the form of manual counterpressure of the deformities was begun, and it was employed daily until Feb. 10, 1941, when a cylindric plaster of paris cast, designed to exert continuous corrective force by means of wedges at the level of the deformi-

ties, was applied to each leg (fig. 6 *B*). Except for one period of six weeks when he had measles and another of eight weeks when he had chickenpox, the use of wedging casts was continued until Feb. 2, 1942, at which time his deformities

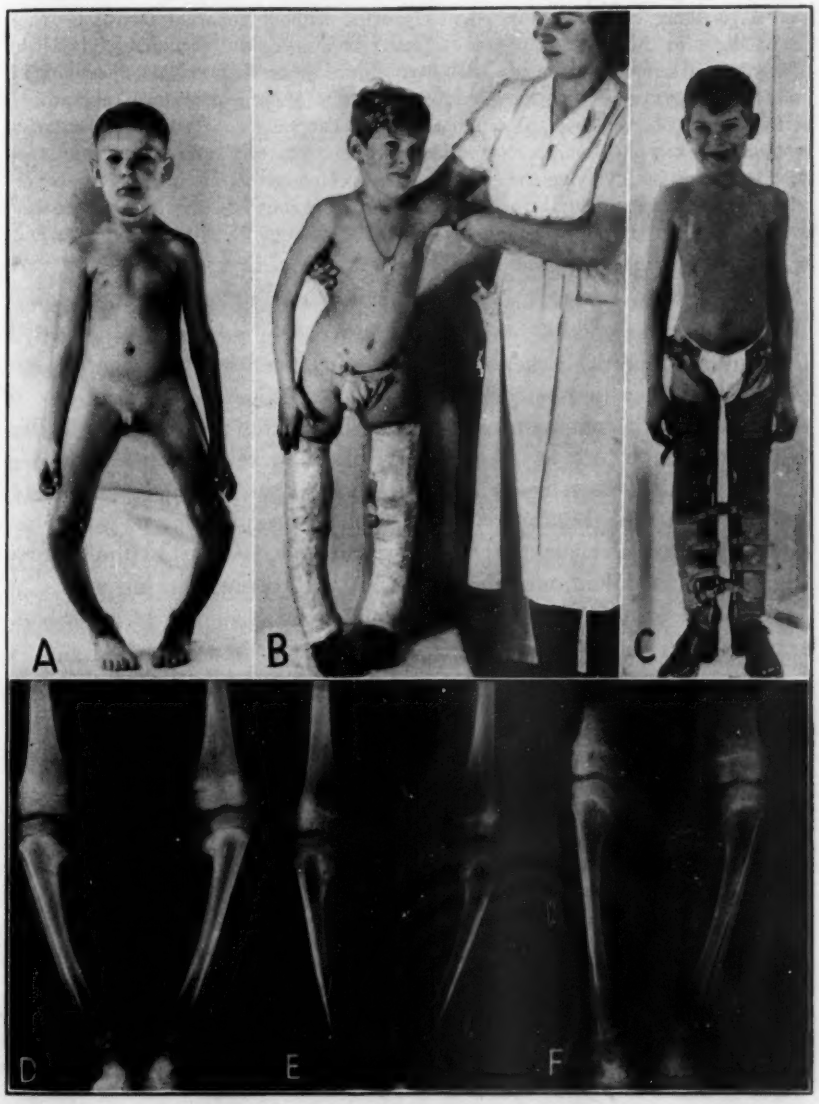

Fig. 6.—T. G., aged 5 years. *A* shows the deformity before treatment was commenced; *B*, wedging casts applied, and *C*, corrective braces applied. *D*, *E* and *F* are serial roentgenograms.

appeared to have been mostly corrected. The wedging force was usually supplemented by means of turn buckles incorporated in the cast on the medial side of each leg. On February 2 supporting casts to maintain correction were applied,

and on February 4 walking was commenced. On March 10 these casts were removed, and during the following week, while braces (fig. 6 *C*) were being made, he was permitted to walk without support.

Although the bowing of the legs has been mostly straightened and standing as well as walking can be performed unsupported without apparent lateral bending, the changes in the tibial epiphyses as interpreted from the roentgenograms have not advanced enough to insure stability. Since it is doubtful whether definite knowledge concerning such interpretation is yet to be had, continued support and further study of this boy's condition are being carried on. Recurrence can most certainly be expected unless correction, through whatever means, is maintained until the condition involving the epiphyses has become arrested. Surgical correction, which seemed unavoidable before treatment was commenced, may still be required to effect lasting correction.

COMMENT

Development of bow leg during childhood still is assigned generally to rickets, even though another cause has been advanced repeatedly.[1] In many communities rickets due to vitamin D deficiency seldom is seen. In such communities osteochondrosis of the upper tibial epiphysis is perhaps the most common cause of acute bending of the legs in children. When a child whose legs have been known previously to have been straight acquires bow leg in the absence of other evidences of rickets, osteochondrosis of the tibial epiphyses should be suspected as the cause. The changes which characterize this condition are revealed by the history, the physical examination and particularly the roentgenograms.

When bowing of the legs can be definitely assigned to osteochondrosis of the tibial epiphyses, further deformity can be prevented and an as yet unknown degree of existing deformity can be alleviated and at times corrected by counterpressure and manipulation if the condition has not become stabilized. Recurrence may be expected if correction, through whatever means, is not maintained until the causative factor has become arrested. Nevertheless, tibial osteotomy may be necessary for the correction of the deformity once arrested.

CONCLUSIONS

Osteochondrosis of the medial half of the upper tibial epiphysis is attended by circumstances so definite as to justify its classification as a separate clinical entity. Although the physical, histologic and roentgenographic changes which characterize this condition are somewhat variable, dependent on the degree of involvement and the patient's age, the clinical symptoms are independent of the age at onset. Gradually increasing bowing occurs, without apparent cause and without the other symptoms of rickets. The deformity is likely to appear bilaterally in the infantile type, frequently with subsequent spontaneous disappearance of the bow leg on one side. In the adolescent type the angulation usually occurs on one side only. There is a limp if the condition is

unilateral and a waddle if it is bilateral. There is an abrupt angulation with the apex laterally just below the knee joint, but in fat children this appears to be a gradual curve (fig. 1). When the deformity appears during infancy, a bulbous enlargement of the medial condyle is palpable on physical examination and visible in the roentgenogram (fig. 2*B*). Recurvation at the knee and relative flatfoot are present, irrespective of the age. Abnormal mobility of the knee on medial strain with normal stability on lateral strain and inward rotation of the tibia on the femur are constantly observed. The roentgenographic (fig. 6*D*) and pathologic changes are like those of coxa plana and similar to those of dyschondroplasia but quite different from those of rickets. Faulty growth of the upper tibial epiphysial cartilage and delayed ossification of its medial half result in a wedge-shaped deformity of this portion of it (fig. 3). The adolescent type looks different in the roentgenogram (fig. 4 *A*). It appears as an arrest of growth rather than a dysplasia. The roentgenographic features of the infantile type gradually change to those of the adolescent type, so that the two can be distinguished later only by the history.

The treatment of osteochondrosis deformans tibiae depends on the stage at which it is instituted. Measures to prevent further deformity or to correct existing deformity, even when extreme, have proved effective during the plastic stage of the condition. When deformity is disabling or unsightly after the osteochondrosis has become arrested, tibial osteotomy is advisable. However, if it is performed before arrest is assured, recurrence of the deformity is to be expected.

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ABSTRACT OF DISCUSSION

DR. LUTHERO VARGAS, Rio de Janeiro, Brazil: Ever since Ollier coined the term and described the first case in 1899, much has been written on dyschondroplasia. The disease can be considered as a retardation of the normal transformation of primordial cartilage into bone. In the words of Ehrenfield, it becomes manifest during the periods of skeletal growth, increases during the period of growth and ceases at the age of skeletal maturity.

The cases of osteochondrosis deformans tibiae fall naturally into two groups: an infantile and an adolescent group. In the former, one must be careful to exclude rickets as a cause of the bowing, and since many of the cases of bilateral involvement occur in the infantile division, it is possible that a mild rachitic state that has not yielded to average doses of sunlight and/or vitamin D plays a role in causation. In this connection, the so-called delayed rickets that may be seen in children up to the age of 10 years must also be remembered. However, the fact that the condition is often unilateral and is occasionally associated with disturbances of osteochondral nature elsewhere in the skeleton, in other words, Legg-Perthes disease, Osgood-Schlatter disease or the aseptic tarsal-scaphoid necrosis of Köhler, would lead one to suspect that the unknown causes of these disorders produce osteochondrosis deformans tibiae.

Although the lesion is undoubtedly a disturbance in enchondral ossification and results in a metaphysial deformity, the superimposed epiphysis is frequently deformed. This might conceivably be explained by a similar disturbance in the line of ossification above the periphery of the epiphysis, but more probably it is due to the differential stress falling on the epiphysis because of faulty weight bearing.

Osteotomy in the metaphysis appears to be a satisfactory treatment. Care must be exercised during the osteotomy and during the subsequent resting in order to prevent abnormal laxity of the lateral ligaments. This can be checked in roentgenograms if the child is still in the growing period, and the possibility of recurrence of the deformity after operation should be explained to the parents. Any discrepancy in length of the legs, which is usually of the order of 1 or 2 cm., is usually corrected by the osteotomy. It appears that the optimum age for correction by osteotomy is from 6 to 9 years for girls and from 7 to 10 for boys, because of the earlier skeletal maturation in girls. It is desirable to observe the patient for a year or so to determine that the deformity is stationary before performing the osteotomy.

DR. WALTER P. BLOUNT, Milwaukee: I must congratulate Dr. Barber on the large group of cases which he has accumulated and on the splendid results which he has obtained. So far as I know, a personal series of 12 cases is the largest that has ever been published.

I decided on the name "osteochondrosis deformans tibiae" as most descriptive of the entity. In this phrase, as Dr. Vargas pointed out, the ending "osis" is used rather than "itis" because the lesion is not an infection but in most cases a variation of the normal physiologic development. The term "tibia vara" was suggested because it is easier to say. It is simple, expressive and not apt to be confusing. It is analogous to coxa vara and cutitus varus and serves to identify the lesion as well as the longer scientific term.

Dr. Barber's last case is most dramatic. He has corrected an extreme bow leg deformity by simple conservative measures. The bony changes as seen in the roentgenogram are still evident, however, and have apparently not kept pace with the cartilaginous and ligamentous changes. I shall be extremely interested in following this case with Dr. Barber to learn if there is sufficient change in the bone later to accomplish a cure without the necessity of operation. It may prove wise in such a case to carry out a preliminary partial correction by conservative means and then perform an osteotomy to complete the cure.

In true tibia vara, as illustrated by the last case, only the medial portion of the proximal tibial epiphysis is involved. The condition in Dr. Barber's first case is a variant, in which there is also involvement of the distal tibial and the distal femoral epiphyses. The deformity is made up of several components. All patients with such a condition whom I have observed have recovered spontaneously.

Like any exaggeration of a "physiologic deformity," infantile tibia vara has a great tendency to recover spontaneously. In enthusiasm for a form of therapy one must not be guilty of the fallacy implied by B. W. Sippy in his famous quip: "The fly sat on the axle of the chariot and said, 'What a dust I do raise!'" One must not be too sure that the improvement obtained is the result of the treatment. Recently I treated bilateral tibia vara in a 2 year old child with wedged casts, and there was dramatic improvement. Whether the same thing would have been accomplished more gradually without corrective casts, I cannot say.

In the management of such conditions, I suggest a period of observation. If one or both legs become more bowed instead of less, conservative treatment should certainly be tried. Dr. Barber has made a real contribution in pointing out the dramatic effect of conservative treatment with wedged casts in selected cases. Operation should be reserved for the deformities which resist such treatment and should not be carried out until the deformity is stationary.

But the most important thing is not the exact type of treatment that is afforded but, as Dr. Barber emphasized in his opening sentences, the recognition of the entity and its true significance. One must avoid the pitfall of immediate operation, which is likely to be followed by recurrence.

Dr. H. A. Swart, Charleston, W. Va.: When I read Dr. Blount's paper a number of years ago, I was much interested in this subject. I talked to him again last fall in Cleveland, and at that time I had never seen any patients with this condition. However, such a patient appeared about four months ago—a little girl of 5 years with a typical bowing of the upper part of the shaft of the tibia. I think her condition corresponds to Dr. Barber's adolescent type. The other leg was completely normal, and there was no sign of rickets. Whether or not this child received cod liver oil in the past was not known.

It did not seem to me that any type of conservative measure would benefit this patient; so osteotomy was done through the upper part of the tibia with the base laterally. She wore an ordinary cast for three weeks, at which time a long leg walking cast was applied. At the end of the three month period this was removed, and the roentgenogram showed good alinement and good formation of callus.

Dr. I. William Nachlas, Baltimore: Dr. Barber deserves thanks for calling attention to a condition that exists. This is a lateral bowing of the leg taking place primarily at the upper tibial epiphysis and, as noted in Dr. Barber's illustrations, associated with medial torsion of the tibia. That the condition is not uniformly rachitic deserves to be reemphasized. Every one of us who lived in the rachitic era, particularly those of us who came from the rickets belt south of the Mason and Dixon line, can tell of many patients with similar deformities for whom a diagnosis of rickets was made before 1920 or 1922. As a result of a careful investigation done under the supervision of Dr. Edwards Park, of the Harriet Lane Home, in the years 1931 to 1933, I can state categorically that a large number of these deformities do not have rachitic manifestations and have not been subjected to conditions which would lead to rachitic changes.

What, then, is this condition? Is it osteochondrosis? I wish Dr. Barber would demonstrate and prove this point more clearly. All he demonstrated is the deformity. Anthropologic studies reveal that tibia vara occurs as a stage in evolution. Phylogenetically this is found true in prehistoric man. Ontogenetically, it will be found that the fetus at 8 months has a well defined tibia vara with a lateral bow and medial torsion.

Go into the maternity ward and observe the babies there. Of every hundred babies there, more than 90 will show bow leg with medial torsion.

What, then, changes these legs from the medial torsion and bowing of the eight month fetal stage to the straight legs of adult life? There is a normal developmental correction of this lateral bow and medial torsion, unless through the medium of abnormal stresses and strains the deformities are maintained.

If a child with severe bow leg is fat and heavy and walks prematurely on the legs, the bowing will increase, chiefly at the place where cartilage is present, namely, at the epiphysis; hence tibia vara will develop. If the deformity is

protected in such a way that the epiphysis will grow in the axis of the limb rather than at an angle, the deformity will tend to correct itself with growth.

One does not need to correct most of these conditions by osteotomy. The judicious use of a brace and the avoidance of premature weight bearing on the limbs will help most of the affected legs to straighten as they grow.

DR. C. GLENN BARBER, Cleveland: In answer to Dr. Nachlas' question as to whether this condition is definitely due to osteochondrosis, Blount has already shown by microscopic studies that the changes which accompany this deformity are the same as those which are present in coxa plana and in similar conditions involving bones elsewhere in the body.

A few slides show the conditions with which osteochondrosis deformans tibiae has been confused. The first slide, copied from a modern textbook of orthopedic surgery, is used to illustrate extreme general bowing of the legs in rickets. Although the lateral bending is extreme, it is due to an acute angulation immediately below the knees, the legs elsewhere being relatively straight. Sloping of the medial half of the tibial condyles can almost be visualized here as a cause of the deformities rather than the condition seen in the next two slides, which characterize bow leg due to rickets.

The anteroposterior roentgenogram of a rachitic leg shows a widening of the epiphyses with an irregular flaring and widening of the adjacent metaphysis. The epiphyses present irregular areas of varying density, causing a mottled, or fluffy, appearance. Here, as in the lateral views, the shafts of the bones are bowed.

Next to rickets the condition with which osteochondrosis deformans tibiae has been most often confounded is dyschondroplasia, or Ollier's disease.

The roentgenogram shown in one of these slides appeared among others equally typical in a recent publication entitled "Dyschondroplasia or Ollier's Disease." The beaklike projection on the medial side of the metaphysis and the angulation at this point, together with the sloping medial half of the upper tibial epiphysis and the perfectly straight shaft, are quite different from the roentgenographic picture seen in Ollier's disease, as the next slide clearly shows.

Although originaly described as involving one side only, Ollier's disease is commonly bilateral. Normal ossification of the epiphysial plate on its diaphysial side fails to occur, and irregular masses of cartilage appear farther and farther along the shafts of the bones involved as growth continues. The bones of the arm as well as the short long bones commonly show simultaneous involvement.

Although lateral angulation at the knees together with a beaklike projection at the medial tibial condyle may be present in the achondroplastic dwarf, the short, squat appearance with broadened metaphyses of all the long bones should enable one to make the correct diagnosis of this condition with little if any difficulty.

ADJUSTMENT OF BLOOD OXYGEN LEVELS IN NEONATAL LIFE

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The availability of umbilical arterial and venous blood for sampling has led to a number of studies on the oxygen content of the blood of the human infant at birth,[1] and considerable emphasis has been placed on the importance of such data for deducing certain facts of neonatal physiology. Actually, evidence from umbilical cord blood must be applied with some care, because of the numerous factors inherent in the process of normal delivery and its obstetric modifications, all of which focus their varying effects on the condition of the fetal blood. Thus a wide variation is observed in any series of measurements of the oxygen content of cord blood. With one or two exceptions,[1e,f] however, there has been a fairly close agreement in the average figures obtained. Thus, the average blood from the umbilical vein, the content of which is, of course, "arterial" blood flowing from the placenta to the fetus, is saturated to about 50 per cent of its oxygen-carrying capacity, while the umbilical arteries are returning to the placenta "venous" blood, which averages about 15 per cent saturation. Since the blood of the infant at birth has a capacity of about 21 volumes per cent of oxygen, the 50 per cent level in the umbilical vein means that about 10 to 11 volumes per cent of oxygen is in that blood, while

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Presented at the annual meeting of the American Pediatric Society, Skytop, Pa., May 1, 1942.

From the Departments of Pediatrics and Obstetrics, Harvard Medical School, and the Boston Lying-in Hospital.

1. (*a*) Eastman, N. J.: Fetal Blood Studies: I. The Oxygen Relationships of Umbilical Cord Blood at Birth, Bull. Johns Hopkins Hosp. **47**:221, 1930. (*b*) Haselhorst, G., and Stromberger, K.: Ueber den Gasgehalt des Nabelschnurblutes vor und nach der Geburt des Kindes, Ztschr. f. Geburtsh. u. Gynäk. **102**:16, 1932. (*c*) Bidone, M.: Il contenuto in ossigeno a acido carbonico del sangue dei vasi ombelicali del feto umano, Ann. di ostet. e ginec. **53**:197, 1931. (*d*) Noguchi, M.: A Study on the Gases in the Umbilical Blood, Jap. J. Obst. & Gynec. **19**:328, 1936. (*e*) Smith, C. A.: The Effect of Obstetrical Anesthesia upon the Oxygenation of Maternal and Fetal Blood, Surg., Gynec. & Obst. **69**:584, 1939. (*f*) Goldbloom, A., and Gottlieb, R.: Icterus Neonatorum: Oxygen Capacity and Saturation of Mother and Fetus, J. Clin. Investigation **9**:139, 1930.

the umbilical arteries are carrying blood with about 3 volumes per cent of oxygen back to the placenta. To preserve clarity in the usage of the present paper, figures for oxygen content will be expressed only as percentages of oxygen-carrying capacity. It will be recalled that in ordinary extrauterine existence this value is rather narrowly fixed between about 94 and 96 per cent in the arteries and varies much more widely in the veins, where it averages about 70 per cent.

The oxygen economy in the fetus at the moment of birth cannot be taken as representative of the physiologic status which has obtained until that time in fetal life, although there has been some tendency to accept such an assumption. Unfortunately, there is a lack of agreement in the only actual data available as to the oxygen levels in the cord blood in utero. Eastman's measurements [1a] showed that the blood in a loop of cord withdrawn from the uterus before the birth of the baby at cesarean section was about 64 per cent and 30 per cent saturated with oxygen in the umbilical vein and arteries respectively (oxygen content 13.3 and 6.3 volumes per cent), while Haselhorst and Stromberger,[1b] on the other hand, found that cord blood similarly obtained was much less well oxygenated than that obtained at the time of delivery, indeed was not so well oxygenated. Their values for these determinations were as low as 16 and 4 per cent (oxygen content 3.5 and 0.9 volumes per cent). Barcroft, Kennedy and Mason [2] have brought forward strong evidence from studies on animals which suggests that the figures of Eastman probably come somewhat nearer the fact, in that such low values as those of Haselhorst and Stromberger may have been due to manipulative interference with normal functions. It is not impossible that the normal human fetus in utero may be obtaining blood even more saturated with oxygen than the 64 per cent found by Eastman, but it must be admitted that in the absence of substantiated measurements the oxygen economy of human life before birth remains uncertain.

About the events taking place after birth not much more is known except for the two important facts that the figures for oxygenation of blood at the moment of birth are known as a result of the use of umbilical cord specimens and that the oxygen relationships of later extrauterine existence are a commonplace of biochemical knowledge. What is lacking is data as to the speed and completeness with which the newborn infant achieves the change from the low oxygen levels in the circulation at birth to the 95 per cent and 70 per cent arterial and venous levels of ordinary life. The change is probably the most essential adjustment required of the newborn organism; but, so far as a search of the literature has revealed, no full study of human arterial blood adjustments during the first hours and days of life has ever been made.

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2. Barcroft, J.; Kennedy, J. A., and Mason, M. F.: Oxygen in the Blood of the Umbilical Vessels of the Sheep, J. Physiol. **97**:347, 1940.

Haselhorst [3] took a few samples from the umbilical arteries in the two or three minutes during which they still pulsate after delivery and found that on the average the oxygenation rose to about 45 per cent in the first minute and in one instance to 66 per cent in eighty seconds after respiration began. Brinkman and Jonxis [4] examined blood from flowing punctures in the skin of 5 full term infants aged from 1 to 7 days and found the following values, which suggest that the adjustment of oxygen levels is not very rapid.

Age (Days)	Arterial Oxygen Saturation (per Cent)
1	96
3	77
3	82
5	81
7	82
Average for 5 infants	83.6

A research by Barcroft, Kramer and Milliken [5] on the oxygen saturation of blood in the carotid artery in the newborn lamb yielded such data as would be desirable in knowledge of the human infant. In these animals, if they were allowed to breathe air the saturation rose to 75 per cent in five minutes after the umbilical cord was tied, although the authors believed a level of 95 per cent would probably not be attained before about five hours.

The purpose of the present study was to learn the degree of oxygen saturation of arterial blood which characterizes the neonatal period in general and to measure the speed with which this level is attained after delivery.

EXPERIMENTAL PROCEDURE

A quick and accurate means by which measurements could be made from small and easily available samples of blood was provided by the microcolorimetric method devised by one of us working with Dr. Oliver Lowry and Miss Dorothy Cohen.[6] By its use, the oxygen content and capacity of a blood sample of about 0.2 cc. can be determined within about fifteen minutes. It was proved by experiments with this method that, as demonstrated by Lundsgaard and Möller,[7] blood flowing under oil from a cutaneous incision is practically identical with that obtained from simultaneous arterial puncture. A special technic was devised to avoid any accession of oxygen from the oil used so that blood could be taken up by a syringe and needle as it flowed from a cut made in the infant's heel. A hole was made

3. Haselhorst, G.: Ueber den Blutdruck in den Nabelschnurgefässen, die Ausschaltung des nabelschnur- und plazentar Kreislaufs nach Geburt des Kindes, Ztschr. f. Geburtsh. u. Gynäk. **95**:400, 1929.

4. Brinkman, R., and Jonxis, J. H. P.: The Estimation of Arterial Unsaturations, Especially in Pediatric Conditions, Acta med. Scandinav. **94**:453, 1938.

5. Barcroft, J.; Kramer, K., and Milliken, G. A.: The Oxygen in the Carotid Blood at Birth, J. Physiol. **94**:571, 1939.

6. Lowry, O. H.; Smith, C. A., and Cohen, D. L.: A Microcolorimetric Method for Measuring the Oxygen Saturation of Blood, J. Biol. Chem., to be published.

7. Lundsgaard, C., and Möller, E.: Investigations on the Oxygen Content of Cutaneous (So-Called Capillary) Blood, J. Exper. Med. **36**:559, 1922.

in the side of a glass vessel and sealed with a rubber dam so that the vessel could be filled with oil to a level above that of this aperture. After incision of the heel and after the first few drops of blood had been sponged away, the heel was immersed in the oil and the later drops collected in a tuberculin syringe by way of a needle thrust through the dam.

RESULTS

The first set of data established the oxygen status occurring in the first two weeks of life. It was obtained from a series of 36 normal infants in the nurseries of the Boston Lying-in Hospital, whose blood oxygen values are shown in table 1 and graphically presented in chart 1. The chart includes, for comparison, a series of measurements made in

TABLE 1.—*Oxygen Saturation of Arterial (Cutaneous) Blood in Neonatal and Adult Life*

Subject	Age	Saturation, Percentage	Subject	Age	Saturation, Percentage	Subject	Saturation, Percentage
Baby 1	8 hours	87	Baby 19	3 days	100	Adult 1	98
2	8½ hours	97	20	3 days	98	2	92
3	9 hours	87	21	4 days	97	3	94
4	10 hours	87	22	5 days	91	4	95
5	14¾ hours	90	23	8 days	92	5	91
6	21 hours	89	24	8 days	93	6	94
7	21 hours	97	25	8 days	97	7	92
8	21½ hours	87	26	8 days	91	8	94
9	22 hours	90	27	8 days	90	9	94
10	22 hours	92	28	8 days	99	10	95
11	26½ hours	87	29	9 days	86	11	97
12	31 hours	96	30	10 days	91	12	94
13	2 days	95	31	10 days	98	13	94
14	2 days	90	32	11 days	90	14	95
15	2 days	82	33	12 days	100	15	96
16	2 days	99	34	12 days	93	16	94
17	2 days	97	35	12 days	97	17	93
18	3 days	99	36	14 days	100	18	92
						19	97
Average of 36 babies					93.0	20	97
						21	99
						22	98
					Average of 22 adults		94.7

the same way on blood flowing from punctures in fingers of a group of normal adults. It will be seen that the neonatal blood was fairly well oxygenated and that 23 (64 per cent) of the infants had arterial (cutaneous) blood with an oxygen level as high as or higher than the lowest adult level.

Our next interest was to learn how soon the general oxygen values just mentioned were achieved after delivery. For a series of 31 infants listed in table 2, the oxygen content of the blood in the umbilical arteries and vein at birth was measured, and at short intervals thereafter, 2, 3 or 4 further specimens were obtained from the heel. By this procedure a total of 121 determinations were made, including those on the cord blood. From most of these 31 infants the first specimen was obtained within thirty minutes after birth; from some a sample was taken at fifteen minutes or even sooner. The results are graphically presented

in chart 2. The clear circles, representing the values for umbilical artery blood at birth, scatter from 0 to about 49 per cent, with an average of 16 per cent, whereas it will be noted that in the majority of specimens taken thereafter, charted as solid circles, an elevation of oxygen content occurred with some rapidity. Sometimes the speed of the change taking place was even visible in the increasingly red color of the blood as it flowed during a single sampling. During the first hour 39 determinations were made, of which 5 (12.8 per cent) gave values within the normal adult range; during the second hour the values obtained in about 35 per cent of the 23 determinations had reached that range; and by the third hour 75 per cent of the 8 samples showed adult levels.

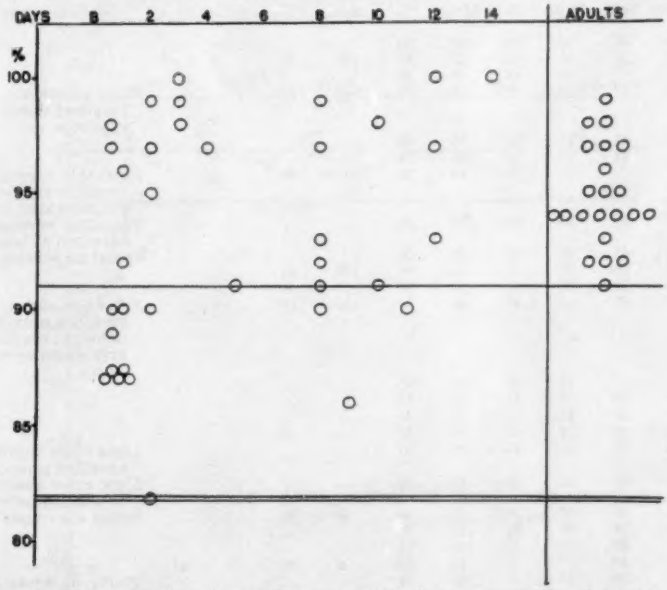

Fig. 1.—Oxygen saturation of the arterial (cutaneous) blood in 36 newborn infants and in 22 normal adults, as in table 1. Ages of infants are shown in days from birth (*B*) to 14. The ordinates show saturation as per cent of oxygen-carrying capacity. The single horizontal line at 91 per cent indicates the lowest level in the normal adult. The double line at 82 per cent indicates the level below which cyanosis might be expected.

It was of interest that no consistent relationship was demonstrated between the level of oxygen in the umbilical artery and the rate of change in the arterial blood after birth. Unusually low or unusually high oxygenation of cord blood seemed to have little specific effect on the oxygen levels thereafter, as may be noted from infants 2, 23, 9 and 12 in table 2.

Although individual curves to connect the rising values for the 31 individual babies studied have not been drawn into the chart, points of

some interest were revealed by the construction of such curves, particularly when roentgenograms of the lungs were taken concurrently with the oxygen measurements. Detailed results for 3 infants are presented to illustrate such studies:

Baby G. was delivered normally under drop ether anesthesia and cried at once, before a roentgenogram could be taken to show the immediate postnatal state of

TABLE 2.—*Adjustment of Oxygen Saturation After Birth*

	Percentage of Saturation of		Cutaneous Specimens: Time After Birth and Saturation								
			Specimen 1		Specimen 2		Specimen 3		Specimen 4		
Baby	Umbilical Artery	Umbilical Vein	Min.	%	Min.	%	Min.	%	Min.	%	Comments
1	18	57	50	86	95	90	...	..	..	..	
2	5	19	15	62	65	81	100	84	..	..	
3	48	83	30	82	65	89	...	..	..	..	
4	19	76	25	67	60	74	240	90	..	..	Ether anesthesia; breathed slowly; some cyanosis
5	20	41	30	82	70	88	...	..	..	..	
6	4	37	20	90	180	94	...	..	..	..	
7	..	..	12	31	40	70	245	89	..	..	Pentothal anesthesia; cyanotic as first sample was taken
8	9	55	20	94	135	96	...	..	..	..	Pentothal anesthesia; breathed at once
9	20	63	20	91	85	94	...	..	..	..	Spinal anesthesia
10	5	70	20	73	75	81	180	93	..	..	
11	20	63	25	74	150	87	...	..	..	..	
12	36	67	15	46	45	56	120	78	..	..	Ether anesthesia, but breathed promptly at delivery; cyanotic as first specimen was taken
13	..	..	15	88	180	95	...	..	..	..	
14	8	30	40	82	90	90	...	..	..	..	
15	24	63	15	85	85	90	...	..	..	..	
16	18	49	18	82	90	87	...	..	..	..	
17	5	47	12	95	20	87	...	..	..	..	Light ether anesthesia; breathed promptly
18	12	34	12	93	45	94	...	..	..	..	Light ether anesthesia; breathed slowly
19	37	75	25	73	30	89	80	93	..	..	Spinal anesthesia
20	7	78	20	86	26	90	...	..	..	..	
21	12	40	20	88	100	91	...	..	..	..	
22	9	40	10	66	14	69	20	81	70	89	
23	0	18	20	86	85	94	...	..	..	..	Thirty-six weeks premature, 3 pounds 15 ounces; no anesthesia
24	..	52	28	86	34	88	98	100	..	..	(Baby P.)
25	16	58	9	63	20	88	95	100	..	..	(Baby G.)
26	49	78	6	10	16	70	29	64	65	81	(Baby C.)
27	..	..	20	88	85	91	...	..	..	..	
28	..	..	105	88	180	93	...	..	..	..	
29	..	..	84	92	155	93	...	..	..	..	
30	..	..	110	80	245	92	...	..	..	..	
31	..	..	80	81	210	92	...	..	..	..	

the thorax. The first film, taken at three minutes, and the next, taken at six minutes, showed such rapid and complete inflation of the lungs that no further films were made. The blood oxygen levels and the times of sampling were as follows:

Time, Min.	Source of Specimen	Oxygen Content (per Cent)
0	Umbilical vein	58
0	Umbilical artery	16
3	(First roentgenogram)	
6	(Second roentgenogram)	
9	Arterial blood from heel	63
20	Arterial blood from heel	88
95	Arterial blood from heel	100

The data and the six minute roentgenogram of this infant shown in figure 3 *A* demonstrate an obviously rapid and satisfactory inflation of the lungs with prompt adjustment of blood oxygen levels.

Baby C. was born by low forceps delivery under drop ether anesthesia and did not breathe for seven minutes thereafter. The protocol of studies on this infant was:

Time, Min.	Source of Specimen	Oxygen Content (per Cent)
0	Umbilical vein	78
0	Umbilical artery	49
1	(First roentgenogram)	
6	Arterial blood from heel	10
7	(Respiration begins)	
10	(Second roentgenogram)	
16	Arterial blood from heel	70
26	(Third roentgenogram)	
29	Arterial blood from heel	64
60	(Fourth roentgenogram)	
65	Arterial blood from heel	81

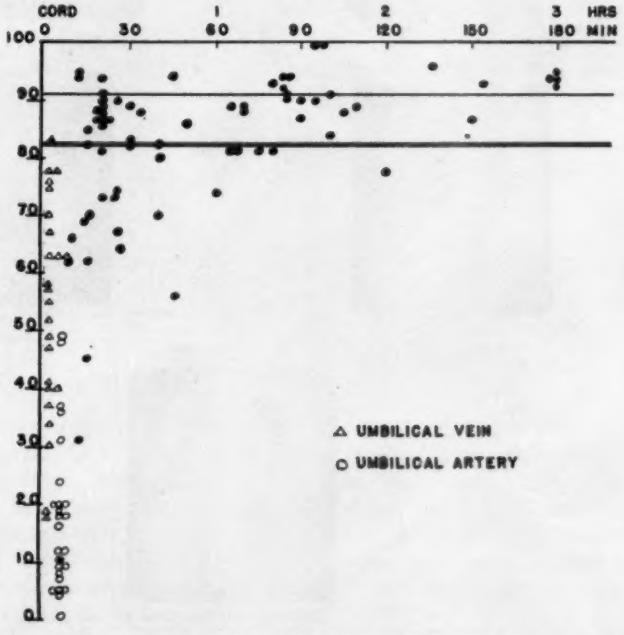

Fig. 2.—Postnatal oxygen adjustment from the data of table 2. One hundred and twenty-one determinations made on 31 infants to show the rise in percentage of blood oxygen saturation (ordinates) from cord blood values during the first three hours of life. The single and double horizontal lines are at the same levels as those of figure 1.

These results are graphically shown in the series of figure 3 *B, C, D* and *E*. Unfortunately this infant was not studied for more than an hour after delivery, and therefore the arrival of the infant's blood at an oxygen saturation of 90 per cent or over was not observed. There is no reason to suppose from the infant's later course that such a state was not reached soon after these studies were done. Irregularity in the upward course of oxygen adjustment after birth, such as the regression

from 70 per cent to 64 per cent between the sixteen and the twenty-nine minute samples, is not infrequently seen, as might be predicted when one considers the lapses into somnolence and lack of response to various stimuli which many babies show in the early hours of life. The roentgenologic and biochemical data show a slower course of adjustment in this subject than in the preceding one; never-

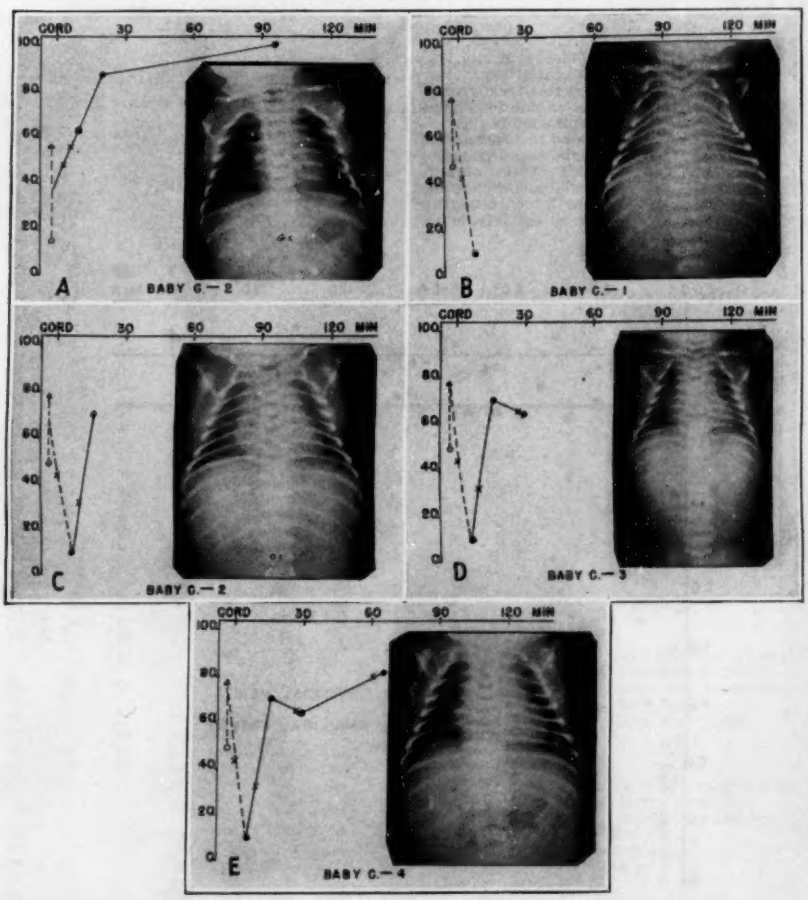

Fig. 3.—*A*, postnatal adjustment in blood oxygen from the umbilical vein (Δ) and artery (O) in baby G (subject 25 in table 2). The roentgenogram, taken at six minutes (the second *X* on the ascending line), shows excellent aeration resulting from prompt breathing at birth. *B*, subject 26 of table 2. Respiration delayed seven minutes. The lines show the oxygen levels of the umbilical vein (Δ) and artery (O), the fall to 10 per cent at six minutes and the time (*X*) at which the roentgenogram was taken. Typical prerespiratory thorax and lungs. *C*, same infant as *B*. Course of blood oxygen saturation during the first sixteen minutes. The roentgenogram (second *X*), taken at ten minutes, shows beginning expansion. *D*, same infant, showing progress of aeration and oxygenation at twenty-six and twenty-nine minutes after birth. *E*, same infant, showing aeration and oxygenation at sixty and sixty-five minutes after birth.

theless the adjustment here is quite satisfactory by comparison with the general data in figure 2 and is rather impressive when one considers that the elevation from 10 per cent to 70 per cent was the result of only the first nine minutes of breathing.

Perhaps most striking were the studies made on baby P. This was a full term infant, born by a normal delivery under anesthesia induced with pentothal sodium. Probably because the dose of anesthetic was large and was administered

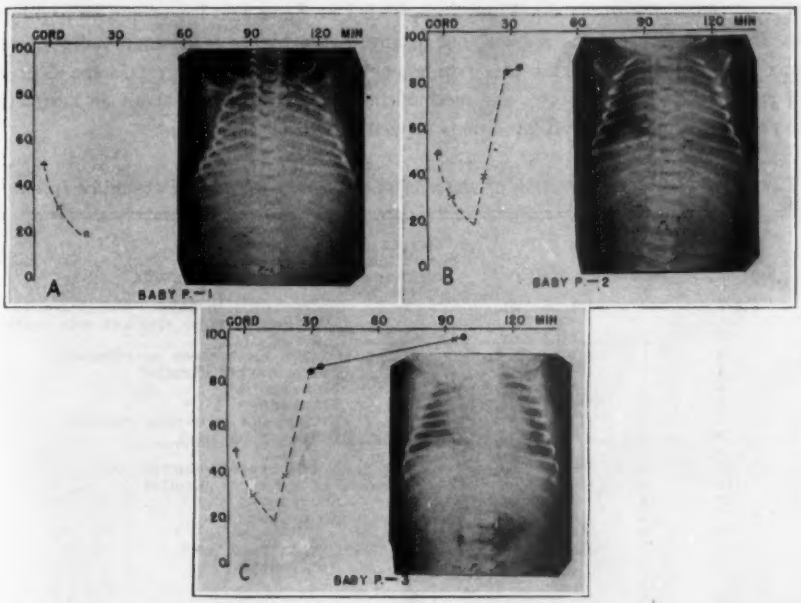

Fig. 5.—*A*, subject 24 of table 2. No sample from the umbilical artery. The roentgenogram (*X*) was taken four minutes after birth. Respiration began at fourteen minutes, indicated by *R*. *B*, same subject, showing partial aeration at second *X*, eighteen minutes after birth and four minutes after onset of respirations. The two solid dots indicate excellent blood oxygen adjustment at twenty-eight and thirty-four minutes. *C*, same subject, with blood oxygen content of 100 per cent at ninety-eight minutes, although the roentgenogram at third *X*, taken one minute later, shows incomplete aeration.

shortly before birth, the baby made no effort to breathe for a full fourteen minutes after delivery. The sequence of events was:

Time, Min.	Source of Specimen	Oxygen Content (per Cent)
0	Umbilical vein (no artery specimen).....	52
4	(First roentgenogram)	
14	(Respiratory onset)	
18	(Second roentgenogram)	
28	Arterial blood from heel.....	86
34	Arterial blood from heel.....	88
98	Arterial blood from heel.....	100
99	(Third roentgenogram)	

How low the oxygenation of this infant's blood must have fallen after birth can only be guessed. A purely arbitrary line with an entirely arbitrary curve has

been drawn in the diagram (fig. 4 *A*) to indicate that the level could not have started upward until fourteen minutes, when respiration began, as indicated by the letter R. It will be observed that although lung expansion appears to be a good deal less complete (fig. 4 *B*) than in the roentgenograms of the first infant, oxygenation as high as 86 per cent was reached at the time the first arterial specimen was taken, which was only fourteen minutes after the first breath, while at a little over an hour and a half after birth and eighty-four minutes after breathing began, the level of oxygen in the blood reached a figure determined at 100 per cent. The actual level may have been 1 or 2 per cent lower and still within the limits of error of the method, but in any case a highly satisfactory adjustment was made, even though the last roentgenogram (fig. 4 *C*) suggests some degree of atelectasis. The ability of the mechanisms involved to bring about an adequate oxygenation under difficult conditions is well shown by this infant.

TABLE 3.—*Oxygen Saturation of Arterial (Cutaneous) Blood in Premature Infants*

Subject	Age, Days	Weight	Oxygen Saturation, Percentage	Comments
Baby 1	1	3 lb. 1 oz.	77	No cyanosis; in oxygen chamber until 2 minutes before specimen was taken
2	1	2 lb. 12 oz.	87	
3	1	3 lb. 9½ oz.	99	Oxygen mask used; no cyanosis
4	2	4 lb. 10 oz.	92	Not in oxygen chamber
5	2	4 lb. 9 oz.	75	No cyanosis
6	2	4 lb. 9 oz.	89	No cyanosis
7	2	3 lb. 10 oz.	94	Crying; not in oxygen chamber
8	2	3 lb. 1 oz.	90	Oxygen mask used
9	3	4 lb. 3 oz.	93	
10	4	3 lb. 8 oz.	96	Not in oxygen chamber
11	4	3 lb. 13 oz.	96	Not in oxygen chamber
12	4	2 lb. 7 oz.	84	No cyanosis
13	4	2 lb. 3 oz.	84	No cyanosis
14	5	4 lb. 7 oz.	90	
15	5	3 lb. 4 oz.	95	Oxygen mask used
16	7	2 lb. 10 oz.	81	No cyanosis
17	7	3 lb. 14½ oz.	87	
18	8	2 lb. 14 oz.	93	
19	9	4 lb. 10 oz.	84	No cyanosis
20	17	3 lb. 12 oz.	78	No cyanosis
21	20	5 lb. 0 oz.	94	
22	23	3 lb. 1 oz.	87	
23	26	3 lb. 3 oz.	80	No cyanosis
Average of 23 babies.....			88.0	

While only 1 premature infant (baby 23, table 2) has as yet been followed by this technic during the hours immediately after birth, a few such patients have been studied during the early days of life, with results listed in table 3 and presented with the full term infants in figure 5. It is evident that these infants, although in some cases showing a surprisingly good status, nevertheless are obviously inferior in their ability to maintain the blood at what must be considered sufficient saturation with oxygen in terms of the expectation for adults or of the performance of full term infants.

COMMENT

When this work was projected, questions of primary interest were: Does the infant live during the neonatal weeks at a marginal level of oxygen supply, by comparison with the rather well stabilized and well

secured oxygen status of the adult organism? Does the newborn infant perhaps live in a state of what might be called subcyanotic anoxia? These questions seem fairly well answered by the data of table 1 and figure 1, in which, although there is some lag below the adult values, the lag is largely confined to the first two days after birth. Figure 1, like all the other charts, has a double line drawn across it at 82 per cent oxygen saturation to mark the general level of oxygenation in the arterial blood below which Lundsgaard and Van Slyke [8] calculated that cyanosis usually appears. Reference to this chart shows that the infants whose arterial oxygen values are below the adult minimum do exist at a "subcyanotic anoxia," but it also shows that 10 of the 13 such infants discovered

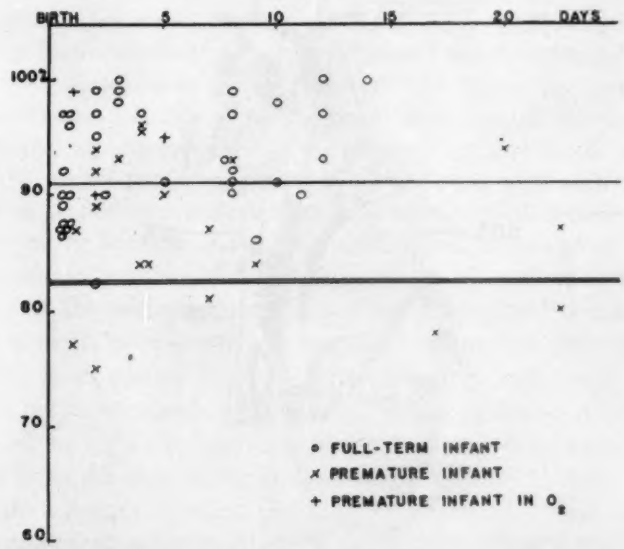

Fig. 5.—Record from data of table 3, showing the oxygen saturation in the arterial (cutaneous) blood of 23 premature infants (*X*) aged from birth to 22 days, as compared with that of the full term infants (*O*) of figure 1. The horizontal lines have the same significance as those in figure 1.

were less than 48 hours old. Satisfactory adjustment of blood oxygenation does not appear to require that the infant must entirely overcome the initial atelectasis of the lungs at birth, although complete proof of this statement would require a roentgenogram of the chest for each of the infants in figure 1 made at the time the blood sample was taken. Such an examination was not made in this group, but from our own experience and from the literature we should expect that at least some of the well oxygenated bloods must have come from the vessels of infants with some degree of atelectasis, since from one third to one half of all

8. Lundsgaard, C., and Van Slyke, D. D.: Cyanosis, Medicine **2**:1, 1923.

infants in obstetric nurseries may have lungs in that condition. Thus Dunham and D'Amico [9] observed that aeration could be called "good" in the lungs of only about 50 per cent of 33 infants roentgenologically studied before the tenth day of age.

It may be stated that oxygen saturation of at least 90 per cent or above is almost the rule in general neonatal life. Do data as to the speed at which this plateau is reached suggest or reveal anything as to the mechanism and timing by which circulatory and pulmonary adjustments are made after delivery? Discussion of this point calls for a

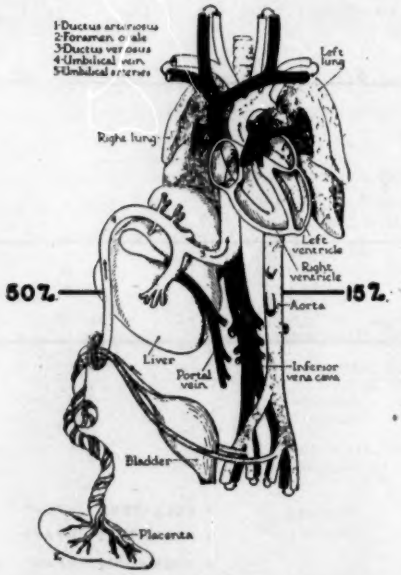

Fig. 6.—The fetal circulation (from Windle [10]), showing the average oxygen concentrations in the umbilical vein and the descending aorta at birth.

brief review of the situation as it obtains up to the moment of birth. A diagram of the fetal circulation [10] (fig. 6) has been labeled to indicate the oxygen saturation in the umbilical vein and in the descending aorta as revealed by umbilical artery samples. No part of the infant's body at birth contains blood any richer in oxygen than that in the umbilical vein, while (with the exception of the liver) all the abdominal viscera and the lower part of the trunk and lower limbs are being supplied with blood no better oxygenated than that in the descending aorta. This will be seen in the diagram to be a mixture of three streams:

9. Dunham, E. C., and D'Amico, M.: A Roentgenographic Study of the Thoraces of New-Born Infants, Yale J. Biol. & Med. **6**:385, 1934.

10. Windle, W. F.: The Physiology of the Fetus, Philadelphia, W. B. Saunders Company, 1940.

(1) a stream (or streams) arriving from the lungs in the left auricle and discharged in the usual manner from the left ventricle; (2) a stream which has crossed through the foramen ovale from the right auricle, and (3) a stream from the right ventricle which has by-passed the lungs by the route of the ductus arteriosus.

Taking these in order, the chemical data certainly speak for an adequate aeration of blood in the lungs, even though the onset of their expansion may not be completed in the anatomic sense within the first few hours (or even days) after it is begun. It is much more difficult to apply the data to the status of the foramen ovale and the ductus arteriosus, since here the question of direction of flow enters. Should the second stream of blood continue to flow through the foramen ovale from the right into the left auricle by reason of any delay in the closure of that orifice, it would obviously dilute the aerated blood returning from the lungs with an addition of venous blood and debase the oxygen level of the mixture. If 30 per cent of the circulating blood should pass through such an unaerated shunt, the resulting mixture should be unsaturated to a degree producing visible cyanosis,[8] associated with an oxygen saturation of perhaps 80 per cent in the aorta. With lessened dilution of blood in the left side of the heart this arterial unsaturation would, of course, be less pronounced. The data of figure 2 suggest that certainly in many of the subjects little or no dilution from such a source could be taking place, even as early as ten or fifteen minutes after birth. On the other hand, should birth be accompanied by sufficiently increased pressure in the left auricle to force blood to leak in the opposite direction (from left to right) through the foramen ovale, no evidence could be derived from the data of figure 2 as to the amount of such a leakage during the adjustment period. Although the eustachian valve supposedly guards against the possibility of a left to right flow, facts as to the pressure relations are not available.

The same problem of direction of flow makes it difficult to apply the chemical data at hand to an understanding of the closure of the ductus arteriosus. It has been shown by Hamilton, Woodbury and Woods[11] that in the animal there is an increase of systolic pressure in the left ventricle as compared with the right immediately on the onset of respiration, a relation which would cause a flow of oxygenated blood from the aorta into the ductus rather than a flow of venous blood through the ductus into the aorta. Again no testimony can be drawn from our data if the only result of slow closure of the ductus should be (as is

11. Hamilton, W. F.; Woodbury, R. A., and Woods, E. B.: The Relation Between Systemic and Pulmonary Blood Pressures in the Fetus, Am. J. Physiol. **119**:206, 1937.

probable) a flow of the latter type. Barclay, Barcroft and others [12] have recently secured roentgenologic evidence that closure of the foramen ovale and the ductus arteriosus in the experimental animal (sheep) follows immediately after the changes in pressure with the first breath.

In summary, all that can be deduced in regard to the neonatal adjustment of circulation and respiration is that no proof has been obtained by these chemical measurements for a gradual type of transformation from fetal to extrauterine mechanisms, so that the transformation must normally be accomplished in such a manner that any relatively prolonged intermediate phase is avoided.

The oxygenation of the blood in the premature infant deserves brief comment, as it indicates a field in which some support of these babies by the generous use of oxygen tents and chambers may well be needed. Brinkman and Jonxis [4] made 14 measurements of arterial blood oxygenation on samples from 7 premature infants aged 1 to 45 days (weights not stated). Their results ranged from 30 to 95 per cent and averaged 64 per cent. Our results agree with these in being below those shown by full term infants, although some of the infants in their series must have been extraordinarily anoxic. It is also surprising that no cyanosis was observed by Brinkman and Jonxis in infants with arterial blood oxygenation reported as low as 45 and 48 per cent. In any case, we are inclined to think that the premature infant's anoxia is most probably a feature of insufficient pulmonary aeration, unless it may be that some peculiarity of the oxygen-combining capacity of the blood itself militates against complete saturation of the premature infant's blood even under conditions satisfactorily utilized by the full term infant. Another subject for speculation is the possibility that just as the premature infant tends to exist at a low level of basal metabolism [13] and may sustain life satisfactorily at low body temperature, so a low oxygen level of the blood may be more suitable to its body economy in the first weeks after birth.

Cyanosis was watched for and occasionally observed in both the premature and the full term infants studied in this paper, but the impression obtained was that it often failed to appear under circumstances which should have produced it. Lundsgaard and Van Slyke [6] calculated

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12. Barclay, A. E.; Barcroft, J.; Barron, D. H.; Franklin, K. J., and Prichard, M. M. L.: Studies of the Foetal Circulation and of Certain Changes That Take Place After Birth, Am. J. Anat. **69**:383, 1941.

13. (*a*) Talbot, F. B.; Sisson, W. R.; Moriarty, M. E., and Dalrymple, A. J.: The Basal Metabolism of Prematurity, Am. J. Dis. Child. **26**:29 (July) 1923. (*b*) Marsh, M. E., and Murlin, J. R.: Energy Metabolism of Premature and Undersized Infants, ibid. **30**:310 (Sept.) 1925. (*c*) Gordon, H. H., and Levine, S. Z.: Respiratory Metabolism in Infancy and in Childhood: XVIII. The Respiratory Exchange in Premature Infants—Basal Metabolism, ibid. **52**:810 (Oct.) 1936.

the threshold of perceptible cyanosis to be a capillary unsaturation of 5 or more volumes per cent of oxygen. In other words, an infant with a blood oxygen capacity of 21 volumes per cent, whose arterial and venous bloods were respectively 80 per cent and 60 per cent saturated (unsaturation 20 per cent and 40 per cent), should show cyanosis by virtue of the following calculation: $\frac{A + V}{2} = \frac{4.2 + 8.4}{2} = 6.3$ volumes per cent capillary unsaturation. One with the same capacity but with 90 per cent and 70 per cent arterial and venous oxygen saturations would have a capillary unsaturation of $\frac{2.1 + 6.3}{2} = 4.2$ volume per cent and, since this is less than 5, should remain of normal color. The venous oxygen levels of our subjects are not known, but we suspect that in those with lowered arterial oxygen content the venous level was almost certainly low rather than elevated, so that in premature infants whose arterial blood was less than 80 per cent saturated, that in the veins must have been well under 70 per cent. But of babies 1, 5 and 23 of table 3, all of whom should on this expectation have shown blueness of the skin, none did so. The implication is that observation of cutaneous color may give misleading evidence as to the oxygen status of neonatal life, but the reason for this is not clear.

Finally, it is suggested that for future studies of obstetric analgesics and anesthetics, of methods of delivery and of other matters affecting the newborn infant data on the speed of adjustment of blood oxygen content may provide more accurate information than data secured from cord blood specimens alone. Judging by the normal infants of figure 2, it appears that a determination of the arterial (cutaneous) blood oxygen in a single specimen taken at perhaps forty-five minutes after delivery would give valuable evidence as to the undisturbed or disturbed functioning of important body adjustments. Although it might be difficult or impossible to select the exact critical level of blood oxygenation below which a definite abnormality was indicated, nevertheless the implications of values above 80 per cent or below 70 per cent might be a good deal more informative than those of measurements obtained only from umbilical cord vessels, which would be subject to the many variables imposed by normal birth itself.

SUMMARY

We have investigated the levels of blood oxygen saturation in normal infants during the first two weeks of life and the time required for the attainment of such levels immediately after birth. The average arterial (cutaneous) oxygen saturation of 36 infants aged 8 hours to 14 days was found to be 93.0 per cent and that of 22 adults 94.7 per cent. The saturation was slightly lower in blood samples taken during the first two days of life than in samples taken thereafter. In a series of 31 deliveries the oxygen saturation of specimens drawn from the umbil-

ical cord vessels and of arterial (cutaneous) specimens taken shortly thereafter showed that the progressive elevation from the low oxygen levels in the cord blood to those of neonatal life is rapidly accomplished. Oxygen saturations within the adult range were sometimes reached in less than thirty minutes after birth and usually within three hours. The rate and degree of this adjustment were not consistently related to the degree of anoxia shown by the cord blood at birth, nor was satisfactory oxygenation necessarily associated with complete expansion of the lungs as shown roentgenologically. In 23 premature infants examined between birth and the twenty-sixth day of life, oxygen saturations were generally lower than those in adults or in full term infants of comparable age. The average saturation of these premature infants was 88 per cent, although a wide scattering of values occurred, ranging from 75 to 99 per cent. Lower levels of saturation were not accompanied by visible cyanosis.

CONCLUSIONS

Although the blood of the normal newborn infant tends to be slightly less oxygenated than that of the adult subject, the infant can hardly be said to exist in a state of subcyanotic anoxia. Such a term may more properly be applied to the status of premature infants.

The immediate postnatal adjustment of blood oxygen content appears to be rapidly accomplished, even in the presence of incomplete pulmonary expansion. The speed with which this is brought about suggests that the rerouting of the circulation at and after birth is performed promptly rather than gradually.

There is little correlation between the state of oxygenation in the umbilical cord blood at the moment of birth and the time required for postnatal adjustment of blood oxygen content in the individual infant.

It is suggested that more valuable biochemical evidence of respiratory and circulatory normality or abnormality in the newborn infant might be obtained by measuring the oxygen saturation of arterial (cutaneous) blood at a stated interval, such as forty-five minutes, postnatally than by studying the blood in the umbilical cord vessels at birth.

Miss Dorothy Cohen made the analyses, and the resident staff of the Boston Lying-in Hospital aided in the collection of specimens of umbilical cord blood.

DISCUSSION

DR. DANIEL C. DARROW, New Haven, Conn.: I was particularly interested to find so many premature infants in the group showing persistent low oxygen saturations. Dr. Stevenson in the laboratory with which I am associated has been determining carbonic anhydrase. He has found that newborn babies are born with low levels of carbonic anhydrase, but that in premature infants the values are even lower, in some cases practically zero. While theoretically a low carbonic anhydrase content might interfere with oxygenation of the blood, it is not known that this is the case, since a low level of carbonic anhydrase would slow the rate of oxygena-

tion of hemoglobin without altering the total uptake for a given oxygen tension. At present there are no satisfactory methods for measuring the rate of oxygenation of hemoglobin. Perhaps future work will show that some babies are cyanotic because of defects in the rate of oxygenation and that they are also defective in carbonic anhydrase.

DR. GEORGE M. GUEST, Cincinnati: As I saw the roentgenograms, it appeared that the pictures were made with the subjects' arms high. I imagine that the blood samples were drawn with the arms at the sides. Can such a difference in position of the infants make a difference in pulmonary ventilation that would affect the oxygen level in the blood?

DR. CLEMENT A. SMITH, Boston: Dr. Roby, the pharmacologist at the Boston Lying-in Hospital, is now working on carbonic anhydrase and is going to do some further studies, using our technic in combination with his own method. He has found exactly what Dr. Darrow says, that the level of carbonic anhydrase seems to be depressed in the blood of premature babies.

Dr. Darrow spoke of these particular premature babies as being cyanotic in certain instances. I should like to say that, although the slides show lines at which cyanosis supposedly occurs, cyanosis in the newborn baby always bears a less exact and predictable relationship to the values from oxygen determinations on the blood than is expected. A number of infants who had the biochemical measurements of cyanosis were not particularly cyanotic in appearance.

I do not know whether I can give a good answer to Dr. Guest's comment. These samples were taken by a deep cut in the heel of the infant, and we insisted that blood flow in a pulsating fashion. If it simply oozed, we discarded the specimen. Whether the position of the arms would have made much difference, I do not know. Considering all the ways in which a baby is moved about after it is born—held up by its feet and slapped and sometimes held in a bath if it does not breathe—it seems as though that might be a rather minor point with regard to routine obstetric procedures.

CONGENITAL MALFORMATIONS INDUCED IN RATS BY MATERNAL NUTRITIONAL DEFICIENCY

II. USE OF VARIED DIETS AND OF DIFFERENT STRAINS OF RATS

JOSEF WARKANY, M.D.

ROSE C. NELSON, PH.D.

AND

ELIZABETH SCHRAFFENBERGER, A.B

CINCINNATI

The appearance of congenital malformations in the offspring of female rats reared and bred on a deficient diet has been described previously.[1] The deficient diet referred to is essentially the Steenbock and Black diet 2965[2] supplemented with viosterol in oil to forestall the development of rickets. This diet, which we call diet 1, has the following percentage composition: yellow corn meal, 76; wheat gluten, 20; chemically pure calcium carbonate, 3, and chemically pure sodium chloride, 1. Sixty U. S. P. units of vitamin D (as viosterol in oil) was administered to each female by pipet every tenth day. Up to the time of writing this report the offspring obtained on this diet consist of 761 young. Five hundred and seventeen of these have been normal and 244 (32 per cent) abnormal. The abnormalities were frequently recognized on external inspection (fig. 1).

The defects of the skeletal system, which have been described in detail in one of our previous publications,[1a] can best be visualized when the animals are cleared by the Schultze-Dawson method (fig. 2). Then there appears in the offspring a definite pattern of abnormalities which is apparently characteristic of the disturbed developmental process caused by the maternal nutritional deficiency.

Read at the Fifty-Fourth Annual Meeting of the American Pediatric Society, Skytop, Pa., May 2, 1942.

From the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati College of Medicine.

1. Warkany, J., and Nelson, R. C.: (*a*) Skeletal Abnormalities in the Offspring of Rats Reared on Deficient Diets, Anat. Rec. **79**:83, 1941; (*b*) Congenital Malformations Induced in Rats by Maternal Nutritional Deficiency, J. Nutrition **23**:321, 1942.

2. Steenbock, H., and Black, A.: Fat-Soluble Vitamins: XXIII, J. Biol. Chem. **64**:263, 1925.

These experiments have been continued and extended. We wish to present here three phases of this work:

1. Experiments concerning the prevention and the failure of prevention of malformations by various dietary supplements.

2. Experiments designed to ascertain the critical period of embryonic development in which the malformations are determined.

3. Experiments on the effect of diet 1 on different strains of rats.

Fig. 1.—*A*, normal newborn rat. *B*, *C*, *D* and *E*, abnormal newborn rats, showing short mandible, protruding tongue, short extremities and syndactylism of the hands.

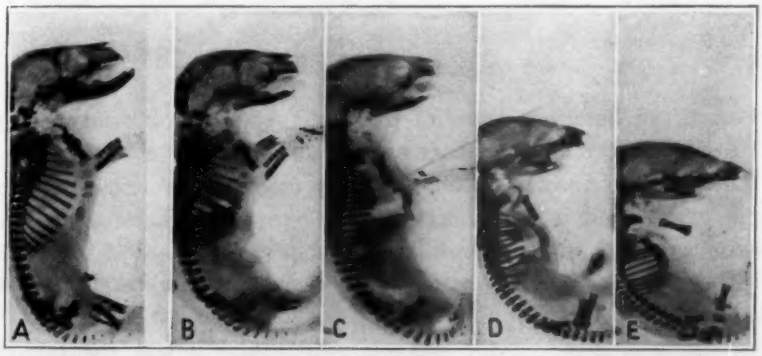

Fig. 2.—*A*, cleared specimen of a normal newborn rat. *B*, *C*, *D* and *E*, cleared specimens of abnormal newborn rats, showing shortness of mandible, shortness or absence of radius, ulna, tibia and fibula and fusion of ribs and of sternal centers of ossification.

DIETARY PREVENTION OF MALFORMATIONS

Since only one third of the offspring of mothers on diet 1 can be expected to be abnormal and since the first litters are less often abnormal than second and later litters, a large number of normal offspring is necessary to prove that a supplement to diet 1 is actually preventive. On

the other hand, it requires only a few abnormal animals to prove that a dietary supplement is not preventive.

Diet 1 is low in iodine, and the mothers reared on this diet as well as their offspring show hypertrophy and hyperplasia of their thyroid glands.[3] It seemed possible that the goiter of the mothers had an influence on the embryonic development of the young. However, table 1 shows that a supplement of iodine in the form of iodized table salt instead of chemically pure sodium chloride in the diet did not prevent the malformations, although the iodine content of this diet was sufficient to prevent goiter in the mothers and their offspring.

The importance of manganese for the development of the skeleton has been emphasized repeatedly. Micromelia in fowls caused by a deficiency of manganese during embryonic development has been reported.[4] The preventive power of manganese was tested in a small number of female rats fed diet 1 supplemented by 0.05 Gm. of manganese

TABLE 1.—*Effects on Offspring of Various Supplements to Diet of Mother*

Mothers Reared on Diet 1 Supplemented by	Offspring		
	Total	Normal	Abnormal
Iodine	91	69	22
Manganese	9	0	9
Casein	231	206	25
Alfalfa leaf meal	55	48	7
Cod liver oil	22	6	16

carbonate per hundred grams of the diet. Addition of manganese to diet 1 did not prevent the malformations (table 1).

Diet 1 supplemented by 10 per cent casein, a protein of animal origin, was tested in a number of female rats and found also to be nonpreventive of malformations of the offspring (table 1). Abnormal offspring were obtained when vitamin-free casein or casein digest[5] was added to diet 1.

Addition of 2 per cent alfalfa leaf meal to diet 1 was also nonpreventive, which is of interest since alfalfa is considered a good source of vitamins A, E and K, riboflavin, pantothenic acid and pyridoxine.

3. Krauss, W. E., and Monroe, C. F.: A Comparison of the Influence of Iodized Milk and of Potassium Iodide Administered Directly on the Size and Iodine Content of the Thyroid Gland of the Rat, J. Biol. Chem. **89**:581, 1930. Levine, H.; Remington, R. E., and von Kolnitz, H.: Studies on the Relation of Diet to Goiter, J. Nutrition **6**:325, 1933.

4. Lyons, M., and Insko, W. M.: Chondrodystrophy in the Chick Embryo Produced by Manganese Deficiency in the Diet of the Hen, Bulletin 371, Kentucky Agricultural Experiment Station, 1937.

5. The preparation used was amigen, supplied by Mead, Johnson and Company.

When the viosterol in oil of diet 1 was supplanted by cod liver oil, abnormal offspring could also be obtained. Each female was given 3 drops of standardized cod liver oil daily in these experiments.

A number of other dietary supplements are now being tested in a similar manner. Among them are the crystalline factors of the vitamin B complex. Although no abnormal offspring have been obtained from the mothers fed such supplemented diets, the figures available are still too small to prove the preventive power of these supplements.

The data now available on the addition of 2 per cent dried pig liver to diet 1 indicate that this supplement does prevent the occurrence of malformations. Similarly an alcoholic extract of liver proved to be preventive if an amount equivalent to 4 Gm. of dried liver was added to 100 Gm. of diet 1 (table 2).

TABLE 2.—*Effects on Offspring of Liver Added to Diet of Mother*

Mothers Reared on Diet 1 Supplemented by	Offspring		
	Total	Normal	Abnormal
Pig liver	322	322	0
Alcoholic pig liver extract	235	235	0

TABLE 3.—*Effect of Addition of Liver to Diet of Rat Having Abnormal Litter on Deficient Diet*

	Offspring	
	Normal	Abnormal
Mother on diet 1	0	4
Same mother on diet 1 plus 2% liver	8	0

The preventive power of liver can also be demonstrated in experiments of alternating diets. If a female rat has had an abnormal litter while on diet 1, the succeeding litter also will be abnormal, as a rule, if the animal is kept on diet 1. However, if the diet of such a female after the first abnormal litter is changed to a liver-containing diet before she is mated again, normal offspring will be obtained regularly in the next litter (table 3).

The addition of liver before the second mating apparently supplies enough of the preventive factor to protect the young of the second litter.

These experiments lead to the second point of the discussion.

EMBRYOLOGIC PERIOD IN WHICH THE MALFORMATIONS ARE DETERMINED

By histologic studies of the embryo one can never ascertain the period in which an injury leading to malformations actually happened, because such studies disclose only the visible end result of the injury.

Consider the different forms of syndactylism seen frequently in the abnormal young. Inspection of rat embryos of various ages indicates that the number of digits becomes recognizable in a 14 day embryo.[6] It may be concluded from this that the development of an abnormal number of digits must be determined before the fourteenth day of fetal life, but one does not learn at which period before the fourteenth day the injury occurred. Theoretically the malformations could be determined in the unfertilized ovum, or at the time of fertilization or at any time after fertilization during the gestation period as late as the fourteenth day.

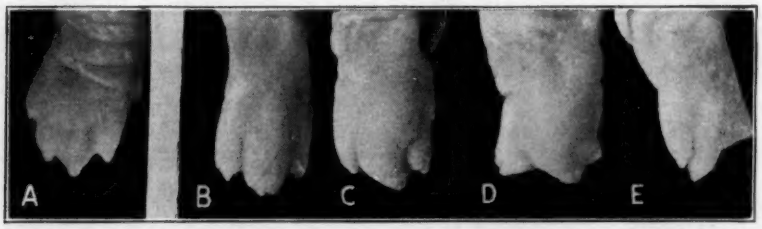

Fig. 3.—*A*, hand of normal newborn rat. *B*, *C*, *D* and *E*, hands of abnormal newborn rats, showing various degrees of syndactylism.

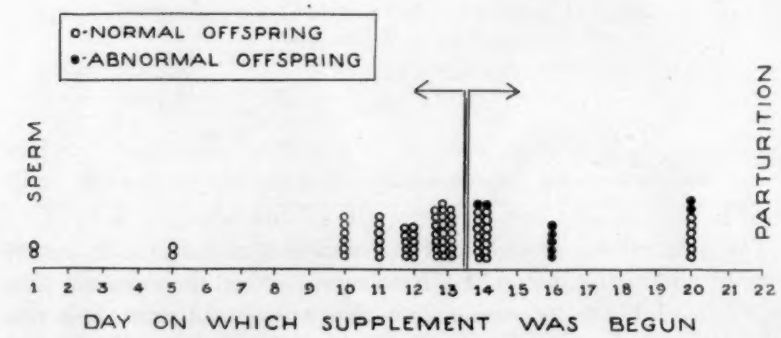
o·NORMAL OFFSPRING
•·ABNORMAL OFFSPRING
SPERM
PARTURITION
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
DAY ON WHICH SUPPLEMENT WAS BEGUN

Fig. 4.—Effect of changes of diet during pregnancy. Female rats reared and bred on diet 1 were given supplements of liver from the day of pregnancy indicated on the abscissa. The supplement was always continued to the time of parturition. The number and type of offspring obtained at term are recorded over the day on which the supplement was begun. The young recorded over days 1, 5, 10, 11, 16 and 20 represent one litter each; the young recorded over days 12, 13 and 14 represent two, four and two litters respectively.

The use of alternating diets just described offered an approach to the answer to this question. It has been mentioned that abnormal off-

6. Long, J. A., and Burlingame, P. L.: The Development of the External Form of the Rat with Observations on the Origin of the Extraembryonic Coelom and Foetal Membranes, Univ. Calif. Publ., Zool. **43**:143, 1938.

spring could be prevented regularly when the change to the liver-containing diet was made before the second mating. We planned then a series of experiments in which the dietary change would be made on different days after mating. Thus we hoped to ascertain exactly the day of gestation before which the offspring could be protected by adding liver to the mother's diet and after which such protection would be impossible. The gestation period of the rat is twenty-two days. In these experiments as planned a rat that has had an abnormal litter on diet 1 will receive the liver supplement one day after her second mating, another rat at two days, a third rat at three days after the second mating, etc., until such experiments with alternating diets have been performed for each of the twenty-one days after conception.

TABLE 4.—*Abnormal Offspring of Female Rats of Different Strains Reared on a Deficient Diet*

Strain	Number of Females	Percentage of Abnormal Offspring
Baltimore	22	30
Wistar	21	0

TABLE 5.—*Fecundity of Two Strains of Rats on a Deficient Diet*

Strain	Number of Females	No Issue	Offspring		
			Normal	Abnormal	Abnormal (Percentage)
Baltimore	22	2	149	64	30
Wistar	21	20	1	0	0

A small number of experiments of this type have been made. Figure 4 shows that the addition of liver to the maternal diet up to the thirteenth day protected the offspring.

After the fourteenth day the addition of liver to diet 1 did not afford complete protection and abnormal offspring appeared. It seems, therefore, that the developmental period between the thirteenth and the fourteenth day should be considered as the critical period in which the nutritional factor under discussion exerts its influence. The absence or presence of the factor at this short period determines apparently whether or not the malformations appear.

EFFECT OF DIET 1 ON DIFFERENT STRAINS OF RATS

The experiments so far reported were undertaken with albino rats of the Sprague-Dawley strain. It seemed of interest to find out how other strains of rats would reproduce under similar dietary conditions.

Dr. L. Emmett Holt supplied a strain of rats which had been inbred in Baltimore for many years. This strain consisted of albino and yellow and black hooded rats. Another strain tested was the Wistar albino strain, obtained from the Wistar Institute in Philadelphia. Twenty-two females of the Baltimore strain and 21 females of the Wistar strain were reared on diet 1, and attempts were made to breed them on this diet. About one third of the offspring of the Baltimore strain were abnormal. No abnormal offspring were obtained of the Wistar strain (table 4). However, it would be erroneous to explain this difference by the genetic purity of the Wistar strain. The explanation is given by table 5. While the females of the Baltimore strain could be reared and bred on diet 1 like those of the Sprague-Dawley strain, the females of the Wistar strain developed very poorly on diet 1. Few of them reached maturity, and only 1 female had a litter, consisting of 1 normal young. No doubt the Sprague-Dawley and the Baltimore strain proved more vigorous and hardy than the Wistar strain under the adverse conditions of diet 1. These hardy strains reproduced on diet 1 and produced a large number of both normal and defective offspring, while the Wistar strain died out.

One might use these observations to refute the conclusion that a given stock is always biologically inferior when congenital malformations appear. In fact, the results of breeding these different strains of rats under adverse environmental conditions indicate that the appearance of malformed offspring rather than none at all may be a sign of hardiness and vigor.

Children's Hospital.

VITAMIN D AND FLUORINE

A SYNERGISTIC RELATIONSHIP?

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NEW YORK

The incidence and prevalence of dental caries among groups of children seem related to many factors. It has been shown that the resistance of children to caries is increased when they are fed certain specified amounts of vitamin D [1] and that improving the diets as a whole also leads to greater resistance to the disease.[2] Children who have been raised in communities where the water supplies are "hard" have lower rates of decay than those using "soft" waters.[3] The fluorine content of communal water supplies seems to be definitely related to resistance to caries in children; the greater the amount of fluorine—within the optimum limits—the greater the resistance.[4]

From DeLamar Institute of Public Health, College of Physicians and Surgeons, Columbia University.

1. (*a*) McBeath, E. C.: Experiments on the Dietary Control of Dental Caries in Children, J. Dent. Research **12**:723, 1932; (*b*) Nutritional Control of Dental Caries, New York State J. Med. **18**:1086, 1933; (*c*) The Influence of Diet on Caries in Children's Teeth (Final Report), Medical Research Council, Special Report Series, no. 211, London, His Majesty's Stationary Office, 1936. (*d*) Anderson, P. G.; Williams, C. H. M.; Halderson, H.; Summerfeldt, C., and Agnew, R. G.: The Influence of Vitamin D in the Prevention of Dental Caries, J. Am. Dent. A. **21**:1349, 1934. (*e*) McBeath, E. C., and Zucker, T. H.: The Role of Vitamin D in the Control of Dental Caries in Children, J. Nutrition **15**:547, 1938. (*f*) Brodsky, R. H.; Schick, B., and Vollmer, H.: Prevention of Dental Caries by Massive Doses of Vitamin D, Am. J. Dis. Child. **62**:1183 (Dec.) 1941.

2 Boyd, J. D., and Drain, C. L.: The Arrest of Dental Caries in Childhood, J. A. M. A. **90**:1867 (June 9) 1928. Boyd, J. D.; Drain, C. L., and Nelson, M. V.: Dietary Control of Dental Caries, Am. J. Dis. Child. **38**:721 (Oct.) 1929.

3. Forberg, E.: Proceedings Third International Dental Congress, Paris, 1900; Dent. Cosmos **43**:360, 1901. Rose, C.; Erdsalzarmut und Entartung, Deutsche Monatschr. f. Zahnh. **26**:1, 1908. Cook, J. B.: The Effects of Drinking Water upon the Causation of Dental Caries in School Children, Lancet **1**: 888, 1914. East, B. R.: Association of Dental Caries in School Children with Hardness of Communal Water Supplies, J. Dent. Research **20**:323, 1941.

4. Dean, H. T.: Endemic Fluorosis and Its Relation to Dental Caries, Pub. Health Rep. **53**:1443, 1938; Fluorine, Mottled Enamel and Dental Caries, J. Pediat. **16**:782, 1940. Armstrong, W. D., and Brekhus, P. J.: Possible Relationship Between the Fluorine Content of Enamel and Resistance to Dental Caries, J. Dent. Research **17**:393, 1938.

In 1933, Hauck, Steenbock and Parsons reported that the addition of fluorine to a rachitogenic diet of rats increased the total bone ash in those animals as compared with the amount in animals which were fed the rachitogenic diet alone and that the addition of both fluorine and vitamin D increased the total bone ash more than did the addition of either one alone.[5] These observations have been confirmed recently by Morgareidge and Finn.[6]

It is suggested that the results obtained in these experiments on animals may have a bearing on the resistance to caries of children residing in areas where water-borne fluorine and high solar ultraviolet energy jointly prevail; such a relationship may also affect the vitamin D requirements of those children.

The principal source of vitamin D, as supplied from nature, is the action of solar ultraviolet energy on the steroids in the bodies of man and animals. The total amount of vitamin D which is formed in this manner is related to (1) the intensity of the solar energy reaching the skin and (2) the length of time the skin is exposed to that energy. The principal factor determining the intensity of solar energy is the latitude of the place where the exposure occurs, while the time of exposure is related to the number of hours of sunshine prevailing, i. e., the number of clear and cloudy days.

Epidemiologic studies indicate that a negative relationship exists between high hours of sunshine, low latitudes and high caries rates.[7] The probability that these observations are valid is strengthened by results from controlled studies among groups of children, in which children who were exposed to artificially produced ultraviolet energy had significantly less new carious tooth surfaces than did the children in the control group, who were not so exposed.[10] Both groups lived in the same institution and consumed the same food and water. The only known variable in the experiments was the extra vitamin D made available to the subjects in the experimental group. The vitamin D involved in these experiments was identical chemically and in its physiologic action with that resulting from exposure to sunshine.

Epidemiologic studies of the relation of fluorine intake and resistance to caries have been widely conducted.[8] There seems little reason to doubt

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5. Hauck, H. M.; Steenbock, H., and Parsons, H. T.: The Effect of the Level of Calcium Intake on Calcification of Bones and Teeth During Fluorine Toxicosis, Am. J. Physiol. **103**:489, 1933.

6. Morgareidge, K., and Finn, S. B.: Effect of Fluorine on the Activity of Vitamin D in Rachitic Rats, J. Nutrition **20**:75, 1940.

7. East, B. R., and Kaiser, H.: Relation of Dental Caries in Rural Children to Sex, Age and Environment, Am. J. Dis. Child. **60**:1289 (Dec.) 1940. East, B. R.: Relation of Dental Caries in Children to Sex, Age and Environment, Am. J. Dis. Child. **61**:494 (March) 1941.

8. Volker, J. F., and Bibby, B. G.: The Action of Fluorine in Limiting Dental Caries, Medicine **20**:211, 1941.

that an intake of fluorine by the mother and her child is associated with a relatively high resistance to caries in the child. These observations are supported by the results obtained in experiments on animals.[8]

With the foregoing facts in mind, it may be worth while to examine the opportunity for the suggested synergistic relationship between fluorine and solar-created vitamin D to take place among children residing in various parts of the United States. In figure 1 are shown the localities in which prevalence of fluorine has been reported.[9] In figure 2, United States Weather Bureau Sunshine Map 13 is reproduced.[10] When the locations of the areas "where mottled enamel has been demonstrated by surveys and/or recorded in the literature" and the "areas where endemic mottled enamel has been reported but not verified" are studied together with the sunshine map, one is struck with two circumstances: First, many of the fluorine areas occur in localities having high annual hours of sunshine; second, many of the fluorine districts, as far as they have been reported, occur in the lower latitudes.[11]

The foregoing observations seem to establish that the following conditions go hand in hand in the United States: (1) A great number of the reported fluorine areas are located where the higher amounts of vitamin D–producing sunshine prevail; (2) a great number of the reported fluorine areas are located in the lower latitudes, and (3) two of the northern areas where fluorine has been reported, the Dakotas and Iowa, enjoy climatic conditions which are particularly effective in distributing ultraviolet energy for cutaneous exposure during the winter months.

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9. It is recognized that water supplies having a fluorine content below the mottling threshold may be effective in raising resistance to caries. In this discussion, it has been assumed that the distribution of fluorine in sufficient amounts to cause mottling would also give a fair index of areas where some water supplies would contain lesser amounts.

10. Weather Map 13, United States Department of Agriculture, Weather Bureau, 1936; Atlas of American Agriculture, United States Department of Agriculture, Weather Bureau, 1936.

11. A special word should be said about the Dakotas, where low caries prevalence rates have been reported. Although the latitudes of the Dakota fluorine areas are relatively high, which would tend to lessen the intensity of the prevailing solar radiation, it is believed that the total amount of ultraviolet energy which would be available for cutaneous exposure over a year's period would equal and possibly surpass that of some of the more southerly communities. It has been demonstrated that clean snow reflects as much as 100 per cent of the available solar ultraviolet energy. This reflection is particularly effective in the higher latitudes, where the sun's rays reach the earth's surface at a low angle. The Dakotas enjoy one of the longest snow covers in the United States, having on the average ninety days per year. These localities are relatively free from heavy industry and relatively thinly populated. Both these conditions tend to keep the surface of the snow clean and able to reflect the solar energy with a high degree of efficiency. The same conditions tend to prevail in the Iowa fluorine districts.

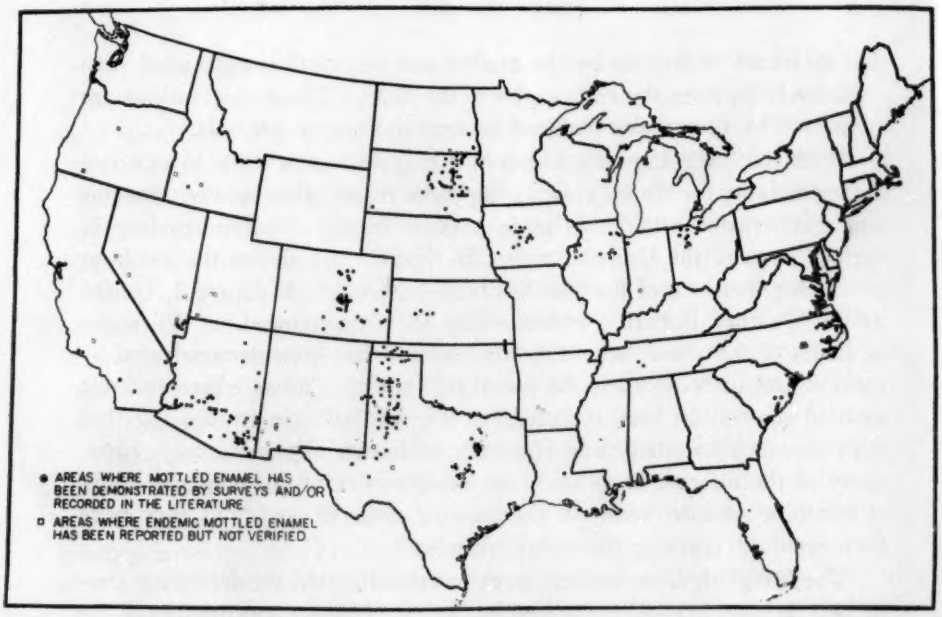
● AREAS WHERE MOTTLED ENAMEL HAS BEEN DEMONSTRATED BY SURVEYS AND/OR RECORDED IN THE LITERATURE
□ AREAS WHERE ENDEMIC MOTTLED ENAMEL HAS BEEN REPORTED BUT NOT VERIFIED

Fig. 1.—Geographic distribution of mottled enamel in the United States in August 1938. (Map furnished by Dr. H. Trendley Dean.)

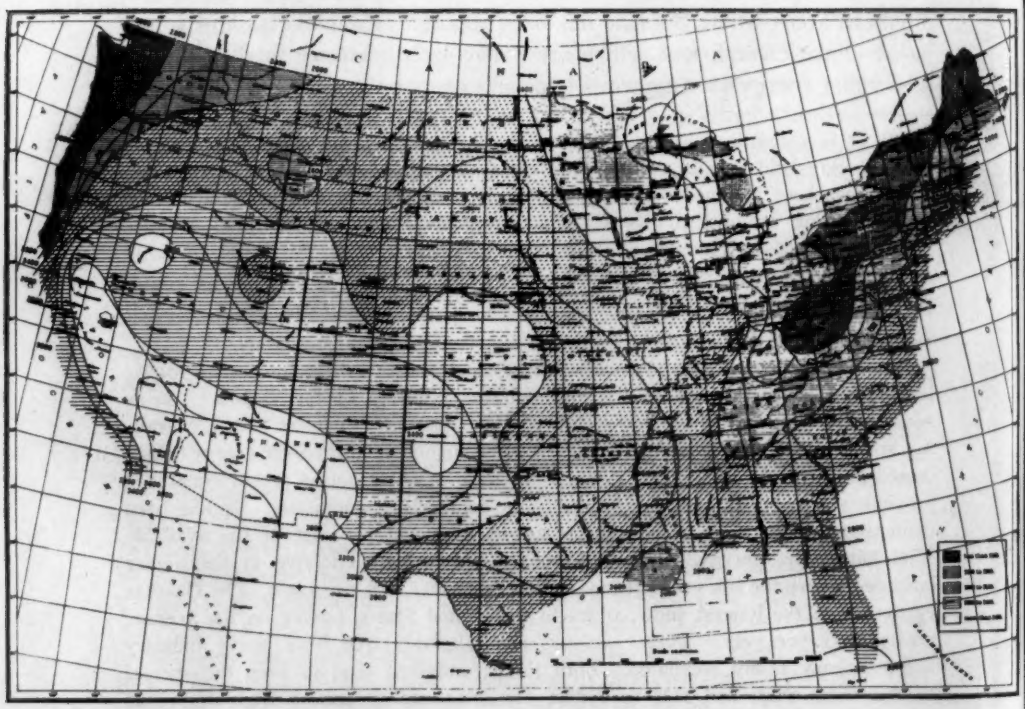

Fig. 2.—United States Department of Commerce, Weather Bureau map 13, showing mean annual amount of sunshine in hours.

If the synergistic relationship between fluorine and vitamin D intake observed in animals holds true for children also, it appears that the geographic distribution of fluorine and solar vitamin D–producing energy is favorable for it to occur.

It is suggested that this relationship might be given consideration when the possible causes for high resistance to caries among some children are being investigated.

It is thought, moreover, that this relationship may, at least in part, account for differences in the minimum daily requirement of vitamin D for infants and children reported by investigators working in different areas of the United States.

NOTE.—Since this paper was written, the observations of Kemp and Nelson [12] have come to my attention. By means of line tests and ash determination on the tibias of rats which had been fed a rachitogenic diet, they too found an increased calcification of bones when vitamin D was added to a fluoride-containing ration. If the ration did not contain fluoride, supplements of vitamin D had less effect on calcification.

600 West One Hundred and Sixty-Eighth Street.

12. Kemp, C. A., and Nelson, V. E.: The Influence of Sodium Fluoride upon the Composition of Tibiae of Rats Partially Recovering from Rickets, Proc. Iowa Acad. Sc. **48**:199, 1941.

CONGENITAL ATRESIA AND STENOSIS OF GREAT CARDIAC VESSELS

AORTIC ATRESIA; PULMONARY STENOSIS

J. I. ROSSMAN, M.D.*
CHICAGO

Two hearts with congenital malformations were examined in autopsy material at St. Luke's Hospital within a short time. In one, there were atresia of the aortic valve, hypoplasia of the left auricle, ventricle and aorta, a patent foramen ovale, a patent ductus arteriosus and an intact interventricular septum. Maud E. Abbott[1] recorded 12 almost identical conditions in her atlas. Since then 4 others have been described. This one is the seventeenth cardiac malformation of this type to be recorded.

The second anomalous heart had a stenosis of the pulmonary valve, hypertrophy of the right ventricle, a patent foramen ovale, a patent ductus arteriosus and an intact interventricular septum. Though pulmonary stenosis complicating some other gross congenital cardiac anomaly is not unusual, anomalous hearts with a combination of defects similar to those in the heart described here are much rarer. This report is the eighteenth record of this form of cardiac malformation.

REPORT OF CASES

CASE 1.—*History and Course.*—A full term white girl was delivered spontaneously at St. Luke's Hospital on Sept. 20, 1941. The primiparous mother, aged 37 years, had mild acute rhinitis on admission to the hospital. She had had measles, mumps and whooping cough during childhood. Her past history, pregnancy and results of physical examination were otherwise irrelevant. The infant's birth weight was 6 pounds 11 ounces (3,033 Gm.). Respiration began normally, but shortly afterward there was a moderate cyanosis, aggravated during feeding or crying. At the age of 1 day respirations were slow and labored. Breath sounds were present over the lungs, and there were many rhonchi and rales. The heart seemed enlarged. The cardiac sounds were distant, and the second sound was everywhere prolonged. A diagnosis of congenital cardiac disease was made. The infant grew progressively worse and died at the age of 4 days.

Autopsy.—The only significant abnormalities were in the heart. The pericardium and epicardium were smooth. The heart was 3.5 cm. in diameter across the base, 3.5 cm. along the left border and 2.5 cm. along the right border. It was 2 cm.

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* John Jay Borland Fellow in Pathology.
From the Henry Baird Favill Laboratory of St. Luke's Hospital.

1. Abbott, M. E.: Atlas of Congenital Cardiac Disease, New York, American Heart Association, 1936.

thick at the base and 1.5 cm. at the apex. There were no changes in the root of the pulmonary artery. The circumference of the pulmonary valve under slight tension was 2.2 cm. The leaflets were thin and occupied normal positions. The right ventricle was large and roomy (fig. 1 *a*). From the attachment of the pulmonic leaflets to the apex it measured 2.7 cm., and from the attachment of the tricuspid leaflets to the apex it was 3 cm. The thickness of the right ventricle anteriorly, midway between the apex and the pulmonic ring, was 0.5 cm. The papillary muscles were hypertrophied. The endocardium was thin, glistening and transparent. The tricuspid ring (fig. 1 *b*) under slight tension was 4 cm. in diameter.

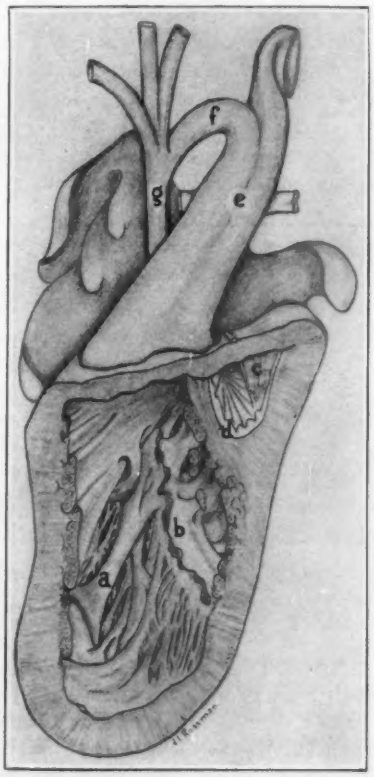

Fig. 1.—Diagram of an anomalous heart with atresia of the aorta, showing (*a*) the right ventricle; (*b*) the tricuspid ring; (*c*) the stenosed mitral ring; (*d*) the hypoplastic left ventricle; (*e*) the pulmonary artery; (*f*) the ductus arteriosus, and (*g*) the hypoplastic aorta.

The free edges of the leaflets were slightly thickened by translucent fibrous tissues. The right auricle was roomy. Its greatest circumference was about 6 cm. It received the superior and the inferior vena cava normally. The foramen ovale was patent, and its orifice, 0.4 cm. in diameter, was guarded by a valvelike fibrous fold extending anteriorly from the inferoposterior wall of the auricle. The left auricle was small, its greatest circumference being 2.5 cm. The endocardium lining the auricle was smooth, thick, white and glistening. The pulmonary veins entered normally, and free communication existed between the

auricles through the patent foramen ovale. The mitral ring (fig. 1 *c*) under slight tension was approximately 0.9 cm. in circumference. The anterior and posterior leaflets were thickened, nodular fibrous tissue partially fused together. They extended into the left ventricle a distance of 2 mm. There were only a few short fibrous chordae tendineae. The papillary muscles were buried in the wall of the left ventricle. On approximating the cut edges, it was apparent that the mitral orifice was, at the most, 1 mm. in diameter. The left ventricle (fig. 1 *d*) was a small cavity buried in the thick musculature of the left wall of the heart. The anterior wall had an average thickness of 0.7 cm., and the posterior wall of 0.5 cm. There was no membranous portion of the interventricular septum. The greatest transverse diameter of the ventricle was 0.8 cm. From the mitral leaflets to the apex, it was 0.6 cm. The endocardium was 1 to 2 mm. thick, yellow-white and glistening. The aortic ring was completely occluded by this thick endocardium. Viewed from above (fig. 2) the aortic leaflets form a fused fibrous diaphragm on the upper surface of which were three crypts, each about 1 mm. deep. In the two anterior crypts, the small coronary ostiums were situated normally. The large vessels at the base of the heart arose normally. The pulmonary artery

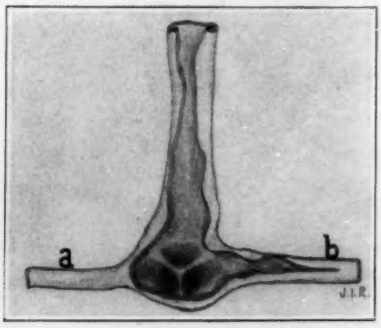

Fig. 2.—Diagram of the aorta (case 1), showing the fused aortic leaflets: (*a*) the right coronary artery; (*b*) the left coronary artery.

(fig. 1 *e*) was large. The diameter was 1 cm., and after giving off the left and right pulmonary arteries it continued through a widely patent ductus arteriosus to join the arch of the aorta. The ductus arteriosus (fig. 1 *f*) was 0.7 cm. in diameter and 0.6 cm. long. The aorta (fig. 1 *g*) was a narrow structure arising behind the pulmonary artery. It was 0.4 cm. in diameter at its origin. From its arch it gave off three large vessels to the neck, each 0.3 cm. in diameter. The aorta just distal to the entry of the ductus arteriosus was larger, 0.8 cm. in diameter. It appeared grossly to be a continuation of the pulmonary artery and ductus arteriosus. The coronary arteries arose as described. They had fine narrow lumens, less than 1 mm. in diameter, and were distributed normally.

Histologic Examination.—There were focal atelectasis peripherally and some hyperemia of the lungs. The epicardium was thin. The myocardium was the usual interlacing striated muscle tissue with large centrally placed vesicular nuclei. There were no aggregates of inflammatory cells, scar tissue or calcification in the many sections examined. The endocardium of the left ventricle was greatly thickened by collagenous connective tissue and a moderate amount of elastic connective tissue, as demonstrated by Weigert and Van Gieson stains. The aortic and mitral leaflets were thin layers of connective tissue without inflammatory exudates or scar tissue thickening.

Anatomic Diagnosis.—The final diagnosis was: congenital atresia of the aortic valve; hypoplasia of the aorta, the left auricle and the left ventricle; mitral stenosis; hyperplasia of the endocardium of the left ventricle; hypertrophy of the myocardium of the right ventricle; dilatation of the lumen of the right ventricle; patent foramen ovale; patent ductus arteriosus; focal atelectasis of the lungs; hyperemia of the lungs.

CASE 2.—*History and Course.*—A white girl was born at St. Luke's Hospital on May 26, 1941. The mother was a primipara aged 25 years. Pregnancy had been entirely uneventful. The onset of respirations was normal, but the infant was a "blue" baby. There was a loud systolic murmur over the precordium. The extremities were cold, blue and edematous. Roentgenographic examination revealed no enlargement of the heart or thymus. Cyanosis was more or less constant and was aggravated by exertion. There was considerable dyspnea. At the age of 9 days the erythrocyte count was 7,730,000 and the hemoglobin content 22.9 Gm. per hundred cubic centimeters of blood. The infant was readmitted to the hospital at the age of 4 months because of increasing cyanosis, dyspnea and dependent edema. The temperature ranged between 96 and 99.3 F.; the pulse rate was 100 and the respiratory rate about 60 per minute. In spite of oxygen and supportive therapy the child died at the age of 4 months.

Autopsy.—The only significant abnormalities were in the heart. The epicardium and pericardium were smooth. The pericardial fluid was normal in amount. Across the base the heart was 4.5 cm. wide and 4 cm. thick. The left border of the heart was 4 cm. long and the right 5 cm. The apex was 1.5 cm. thick. The wall of the right ventricle was hypertrophied (fig. 3 *a*). The average thickness measured anteriorly was 0.8 cm. The papillary muscles were hypertrophied and the endocardium was smooth and glistening. The length of the right ventricle from the attachment of the tricuspid leaflets to the apex was 2.7 cm. The greatest internal diameter of the ventricle was 3 cm. In the region of the pulmonic ring the myocardial and endocardial tissues were fused to form a short, funnel-shaped passage, the apex of which was formed by the fused pulmonary valve leaflets. These formed a domelike diaphragm, in the center of which was a pinpoint opening (fig. 3 *b*) leading into the pulmonary artery. The ventricular endocardium in this region was moderately thick, yellow-white and glistening. The tricuspid ring was 4 cm. in diameter. The leaflets were slightly thickened and nodular and extended into the ventricle a distance of 0.6 cm. The chordae tendineae were short, ranging from 2 to 4 mm. in length. The right auricle received the superior and inferior venae cavae and the coronary sinus normally. The latter was guarded by a membranous thebesian valve. In the interauricular septum posteroinferiorly was an opening, 1 cm. in diameter, leading through an oblique passage, approximately 0.6 cm. in length, into the left auricle. The greatest internal circumference of the left auricle was 8 cm. The left ventricle was also large with a hypertrophied wall. The aortic leaflets were thin. Under slight tension the circumference of the aortic ring was 2.3 cm. The coronary ostiums were patent and were situated normally. The length of the left ventricle from the attachment of the aortic leaflets to the apex was 4.5 cm., and the length from the mitral leaflets to the apex was 3.8 cm. The average thickness of the left ventricular wall measured near the septum behind was 0.6 cm. The greatest internal diameter of the ventricle was 2 cm. The endocardium was smooth and thin. The mitral ring under slight tension was 2.8 cm. There were two ill defined nodular leaflets hanging into the ventricle for an average distance of 0.5 cm. The chordae tendineae were thin, ranging to 0.6 cm. in length. The left auricle received the pulmonary veins

normally. On the medial wall anteriorly and inferiorly was a crescentic valve-like fold, approximately 1 cm. wide, guarding the patent foramen ovale. The large vessels at the base of the heart were normal in origin and position. The pulmonary artery (fig. 3 *c*) was large and roomy, with an average diameter of 1.2 cm. At its origin the pulmonic leaflets were fused to form a dome-shaped diaphragm 0.5 cm. high and 0.3 cm. wide, buttressed on three sides by fibrous thickenings (fig. 3 *b*). At its apex was a pinpoint opening 0.5 mm. in diameter. The root and arch of the aorta were not unusual. The aorta (fig. 3 *d*) was 1.4 cm. in diameter. The large vessels to the neck arose normally, and just distal to the origin of the left subclavian artery there was a widely patent ductus arteriosus (fig. 3 *c*) 0.6 cm. long. At the aortic end the opening was 0.3 cm. wide, and at the pulmonic end it was 0.2 cm. The coronary arteries were normal in origin and distribution. Their linings were smooth.

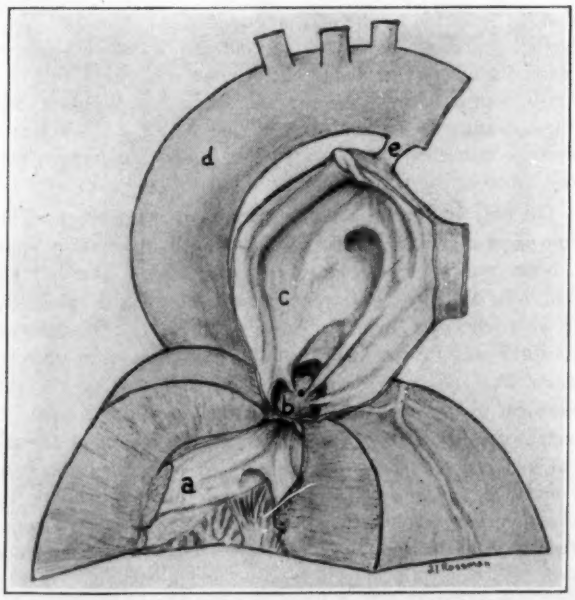

Fig. 3.—Diagram of the anomalous heart with stenosis at the pulmonic ring, showing: (*a*) the hypertrophied right ventricle; (*b*) the fused pulmonic leaflets with a minute opening in the apex; (*c*) the pulmonary artery; (*d*) the aorta, and (*e*) the ductus arteriosus.

Histologic Examination.—There were no evidences in the myocardium of inflammatory exudates, fibrous scars, calcification or degenerative changes of the muscle fibers. The endocardium in the region of the pulmonary stenosis was moderately thickened by collagenous connective tissue with some elastic connective tissue. There were no scars or fibrous tissue thickenings in any of the valve leaflets, including the stenosed pulmonic leaflets.

Anatomic Diagnosis.—The diagnosis was: congenital stenosis of the pulmonic valve; hypertrophy of the wall and dilatation of the lumen of the right ventricle of the heart; patent foramen ovale; patent ductus arteriosus; slight hypertrophy of the myocardium of the left ventricle of the heart.

COMMENT

Congenital stenosis or atresia of the large vessels of the heart occurs usually in one of three forms. These are illustrated diagrammatically in figure 4. One form (fig. 4*a*), first described by Keith [2] in 1909, is caused by the improper involution of the bulbus cordis, the lower margin of which remains as a ledge at the junction of the bulbus and the ventricle. This causes the so-called pulmonary conus type of stenosis

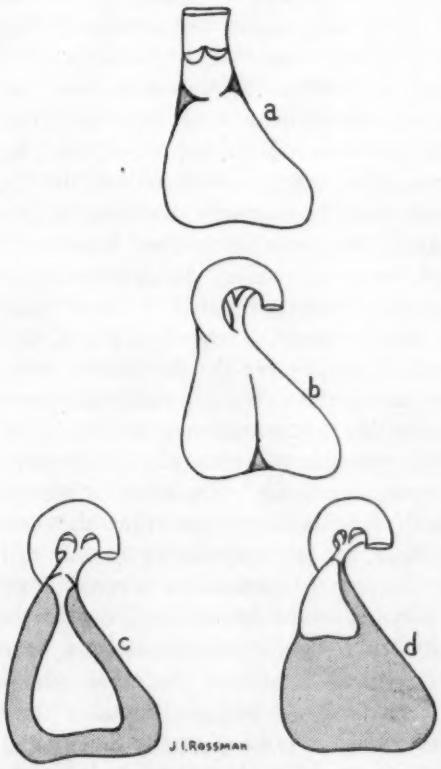

Fig. 4.—Sketch of the various forms in which atresia or stenosis of the great cardiac vessels occurs: (*a*) pulmonary conus or subaortic type of stenosis; (*b*) stenosis or atresia associated with transposition of the great cardiac vessels; (*c*) and (*d*) stenosis and atresia due to fusion of the valve leaflets secondary to asymmetric septal development.

proximal to the pulmonary artery, or the subaortic type of stenosis on the aortic side. In hearts with this abnormality there is a small cavity proximal to the aorta or pulmonary artery; the large vessels and their semilunar valves are normal, and there is frequently a defect of the interventricular septum.

2. Keith, A.: Malformations of the Heart, Lancet **2**:359, 1909; Fate of the Bulbus Cordis in the Human Heart, ibid. **2**:126, 1924.

A commoner form of stenosis, most frequently involving the pulmonary artery, is seen in association with some degree of transposition of the large cardiac vessels (fig. 4*b*). The pulmonary artery is stenosed and frequently bicuspid; the aorta is large, and there is usually a defect of the interventricular septum. Explanations of these anomalous hearts have been advanced on a phylogenetic basis by Spitzer [3] and more recently on an ontogenetic basis by Lev and Saphir.[4]

A third form (fig. 4*c* and *d*) is seen in hearts similar to those described in this report. There is usually no interventricular defect, transposition of the great vessels or associated congenital anomaly. The main lesion is a fusion, partial or complete, of the valve leaflets. The foramen ovale and ductus arteriosus remain open secondarily as a result of disturbed hydrodynamics. If stenosis of the valve is present, the corresponding ventricle will be hypertrophied (fig. 4*c*), but if the condition is atresia, that side of the heart will be hypoplastic, with a diminutive ventricle lined by a greatly thickened endocardium (fig. 4*d*).

The physiology of the circulation in these hearts is of interest. In the case of atresia of the aortic valve, the systemic venous blood enters the right side of the heart normally. It then passes to the lungs, becomes aerated and returns to the hypoplastic left auricle. Very little of this blood, if any, enters the diminutive ventricle. The blood in the left auricle passes through the patent foramen ovale to the right auricle to mix with the nonaerated venous blood. It passes with the latter into the right ventricle and thence is distributed to the pulmonary artery and the ductus arteriosus. The latter is the only outlet through which the partially aerated blood can enter the systemic circulation, and it is usually large, the aorta appearing grossly to be a continuation of the pulmonary artery. Cyanosis is severe. The coronary blood supply is mainly blood from the ductus arteriosus flowing in a retrograde fashion down the aorta. Similar conditions, to a lesser degree, prevail if the condition is one of stenosis of the aorta. In pulmonary atresia or stenosis, the foramen ovale and the ductus arteriosus act similarly as shunts, through which a portion of the nonaerated blood, excluded from the right side of the heart, is aerated and distributed to the body.

The first two types of stenosis or atresia are satisfactorily explained by assuming an arrest or abnormality of growth at some critical stage of morphogenesis, and there are usually other anomalies in the heart and elsewhere as manifestations of the same growth deficiency. The explanation of the third type, however, is more difficult, since superficially the lesion would seem to be the result of a process which involves the heart after it has already developed normally and without congenital

3. Spitzer, A.: Ueber den Bauplan des normalen und missbildeten Herzens, Virchows Arch. f. path. Anat. **243**:81, 1923.

4. Lev, M., and Saphir, O.: Transposition of Large Vessels, J. Tech. Methods **19**:148, 1939.

defects. As an explanation, the concept of an inflammatory process of the myocardium and endocardium, with resultant adhesions, scarring, stenosis and atresia of the valve leaflets, was first introduced by Kreysig in 1816. In more recent years, this concept has been supported by Maud Abbott, who has emphasized that, besides the discreteness of the lesion, the condition of the warty, thickened and deformed leaflets frequently resembles end stage valvulitis. Though histologic studies are scarce, supporters of this view have demonstrated myocardial scars and fibrosis, vacuolar and fatty degeneration, calcification and lymphocytic infiltration of the myocardium, distended capillaries, occasionally with aggregates of leukocytes in their lumens, valvular excrescences and extreme thickening of the parietal endocardium.

Mönckeberg [5] in 1907 was among the first to dispute the contention that inflammation is responsible for many congenital anomalies. Since then others have demonstrated that an intact interventricular septum can occur in grossly anomalous hearts of obvious congenital origin. Though most supporters of the concept of fetal endocarditis state that the source of the inflammation is the mother, yet in most cases the mothers have been perfectly well during their pregnancies. Also no case of acute fetal endocarditis has yet been described. All the lesions apparently are healed. Stohr [6] points out that, in general, fetal valves are seldom the site of infectious lesions, basing this statement on the earlier work of Fischer,[7] who pointed out that embryonal tissues seem to bear a special immunity to infection, apparently due to the lack of cell receptors for toxin. Paul Gross,[8] in an excellent review of the concept of fetal endocarditis, pointed out that all the histologic criteria mentioned as evidence of inflammation can be found in congenital cardiac lesions of obviously noninflammatory origin. He stated that the absence of scar tissue in the deformed valves is a serious objection to the assumption of an inflammatory origin. In both hearts here described there were no histologic evidences of a recent or of an old inflammatory process. The endocardial thickening has generally been conceded by Maud Abbott and others to be a simple noninflammatory hyperplasia of fibroelastic tissue with the exact impulse of development unknown.

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5. Mönckeberg, J. G.: Demonstration eines Falles von angeborener Stenose des Aortenostiums, Verhandl. d. deutsch. path. Gesellsch. (1907) **11**:224, 1908.

6. Stohr, G.: Malformations of the Hearts of the Newborn: Congenital Lesions Suggestive of Inflammatory Origin, Arch. Path. **17**:311 (March) 1934.

7. Fischer, B.: Ueber fötale Infektionskrankheiten und fötale Endokarditis, nebst Bemerkungen über Herzmuskelverkalkung, Frankfurt. Ztschr. f. Path. **7**:83, 1911.

8. Gross, P.: Concept of Fetal Endocarditis: General Review with Report of Illustrative Case, Arch. Path. **31**:163 (Feb.) 1941.

How may the malformations in these two anomalous hearts be explained on a developmental basis? The simplest and most satisfactory explanation was proposed in 1875 by von Rokitansky,[9] who postulated an eccentric position of the septum of the truncus arteriosus, with a resultant unequal division of the bulbus cordis and crowding together of either the pulmonic or the aortic valve leaflets, as the underlying cause of these anomalies.

SUMMARY AND CONCLUSION

The clinical history and the gross and microscopic observations at autopsy in 2 cases of congenital cardiac anomalies are given. One specimen presented atresia of the aortic valve, hypoplasia of the left side of the heart, a hypertrophied and dilated right ventricle, an intact interventricular septum, a patent foramen ovale, a patent ductus arteriosus and pronounced thickening of the endocardium of the left ventricle. The other specimen manifested stenosis of the pulmonic valve, hypertrophy of the right and left ventricles of the heart, an intact interventricular septum, a patent foramen ovale and a patent ductus arteriosus. The commoner forms of congenital stenosis and atresia of large cardiac vessels are outlined and their morphogenesis briefly discussed. The possible role of fetal inflammation in the causation of stenosis and atresia of the type here presented is discussed, and the conclusion is reached that these anomalies arise as developmental errors. There was no histologic evidence of inflammation in either of the hearts described in this presentation. The physiology of the circulation is briefly outlined.

St. Luke's Hospital.

9. von Rokitansky, C. F.: Die Defecte der Scheidewände des Herzen, Vienna, W. Braumüller, 1875.

Case Reports

SICKLE CELL ANEMIA IN THE WHITE RACE

REPORT OF TWO CASES WITH DIAGNOSIS BY SPLENIC PUNCTURE

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Herrick's original description of sickle cell anemia [1] stimulated great interest in its genesis, course and treatment, and various aspects of the disease in Negroes have been reported.[2] Later it was encountered in the white race. Of all reported cases of its occurrence in white persons, only 13 [3] withstood careful scrutiny as to their authenticity with regard

From the Department of Laboratories, Division of Hematology, and the Department of Pediatrics, the Jewish Hospital.

1. Herrick, J. B.: Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia, Arch. Int. Med. **6**:517 (Oct.) 1910.

2. (*a*) Anderson, W. W., and Ware, R. L.: Sickle Cell Anemia, Am. J. Dis. Child. **44**:1055 (Nov.) 1932. (*b*) Beck, J. P., and Hertz, C. S.: Am. J. Clin. Path. **5**:325, 1935. (*c*) Cardozo, W. W.: Immunologic Studies of Sickle Cell Anemia, Arch. Int. Med. **60**:623 (Oct.) 1937. (*d*) Cooley, T. B., and Lee, P.: Sickle Cell Phenomenon, Am. J. Dis. Child. **32**:334 (Sept.) 1926. (*e*) Diggs, L. W.: Am. J. M. Sc. **187**:521, 1932; (*f*) J. Lab. & Clin. Med. **17**:913, 1932. Diggs, L. W., and Bibb, J.: Erythrocyte in Sickle Cell Anemia: Morphology, Size, Hemoglobin Content, Fragility and Sedimentation Rate, J. A. M. A. **112**:695 (Feb. 25) 1939. (*g*) Graham, G. S.: Sickle Cell Anemia with Necropsy, Arch. Int. Med. **34**:778 (Dec.) 1924. (*h*) Hahn, E. V., and Gillespie, E. B.: Sickle Cell Anemia: Report of Case Greatly Improved by Splenectomy; Experimental Study of Sickle Cell Formation, ibid. **39**:233 (Feb.) 1937. (*i*) Steinberg, B.: Sickle Cell Anemia, Arch. Path. **9**:876 (April) 1930. (*j*) Sydenstricker, V. P.; Mulherin, W. A., and Houseal, R. W.: Sickle Cell Anemia: Report of Two Cases in Children, with Necropsy in One Case, Am. J. Dis. Child. **26**:132 (Aug.) 1923. (*k*) Wiener, A. S.: Hemolytic Reactions Following Transfusions of Blood of Homologous Group: Further Observations on Role of Property Rh, Particularly in Cases Without Demonstrable Isoantibodies, Arch. Path. **32**:227 (Aug.) 1941.

3. (*a*) Cooley, T. B., and Lee, P.: Sickle Cell Anemia in a Greek Family, Am. J. Dis. Child. **38**:103 (July) 1929. (*b*) Steinberg.[2i] (*c*) Clarke, F.: Nebraska M. J. **18**:376, 1933. (*d*) Cooke, J. V., and Mack, J. K.: J. Pediat. **5**:601, 1934. (*e*) Greenwald, L., and Burrett, J. B.: Am. J. M. Sc. **199**:768, 1940. (*f*) Haden, R. L., and Evans, F. D.: Sickle Cell Anemia in White Race: Improvement in Two Cases Following Splenectomy, Arch. Int. Med. **60**:133 (July) 1937. (*g*) Pineus, J. B., and Rosenfeld, S.: Am. J. M. Sc. **184**:674, 1932. (*h*) Weiner, S. B.: J. Mt. Sinai Hosp. **4**:88, 1937.

to the presence or absence of sickling, elliptic cells or ovalocytes or whether or not there was evidence of admixture of Negro blood.[4]

The purpose of this report is to point out the value of splenic puncture and the study of splenic tissue for evidence of sickling in those cases in which it is not apparent in the peripheral blood stream and also to record instances of sickling in 2 additional white families. The ancestors of both families were born and lived in Italy. Family F. originated in Vizzini in the province of Catania and family V. in Catanzaro in the province of Calabria. The parents of the patients emigrated to the United States.

REPORT OF CASES

CASE 1.—V., a white girl 4 years old when first seen, was observed in the wards and in the outpatient department of the Jewish Hospital of Brooklyn for a period of approximately seven years. During this time she was admitted to the hospital on six separate occasions. On her first admission, Dec. 4, 1934, she complained of pains in her abdomen and back and frequency of urination. Examination revealed evidences of pneumonia of the lower lobe of the right lung caused by pneumococci type XVII. The urine contained clumps of white blood cells. Examination of the blood showed a hemoglobin content (Haden-Hausser) of 54 per cent, a red cell count of 3,200,000 and a white cell count of 15,000, of which 50 per cent were polymorphonuclear leukocytes. Sickling was not looked for. The patient was not jaundiced. She was discharged after a stay of sixteen days in the hospital.

She was readmitted on Jan. 7, 1935, for pain and swelling of the left hand and right elbow. This stay was complicated by the appearance of varicella, which necessitated her removal to Kingston Avenue Hospital (for patients with contagious diseases). Again sickling was not searched for. The peripheral blood at this time showed a hemoglobin content of 61 per cent, a red cell count of 3,090,000 and a white cell count of 26,000. The urine was normal.

She was admitted for the third time six months later, because of pain and swelling of the right side of the face. This was found to be due to an alveolar abscess, and the offending tooth was extracted. Examination of the blood revealed the following values: hemoglobin content, 61 per cent; red cell count, 2,280,000, and white cell count, 15,000. Sickling was not looked for.

She was followed in the outpatient department from August 1935 to Oct. 17, 1938. During this time she complained of pain in the chest at one time and, after an injury, of pain in the right elbow; evidence of fracture was not found. In March 1936 she complained of pain in the right shoulder. At this time a systolic murmur was heard over the precordium. The blood was not examined for sickling. On two separate occasions she had an attack of abdominal pain resembling acute appendicitis. For the first time, the possibility of sickle cell anemia was entertained, but the peripheral blood did not reveal any evidence of it.

4. (*a*) Archibald, R. G.: Tr. Roy. Soc. Trop. Med. & Hyg. **19**:389, 1926. (*b*) Castana, V.: Pediatria **33**:431, 1925. (*c*) Stewart, W. B.: Sickle Cell Anemia: Report of Case with Splenectomy, Am. J. Dis. Child. **34**:72 (July) 1927.

The fourth admission to the hospital was necessitated because of pyuria. She recovered after a course of treatment with mandelic acid and ammonium chloride. This stay was complicated by pneumonia. The icteric index was 14.3 and was attributed to the pneumonic process. The hemoglobin content ranged from 53 (on admission) to 70 per cent (on discharge) and the red cell count from 2,800,000 to 3,700,000. The blood chemistry was within normal limits.

From October 1936 to July 16, 1938, she made numerous visits to the outpatient department (fig. 1). Her complaints were abdominal pains, pains in the joints and frequency of urination (pyuria). When last seen, on July 16, 1938, she was extremely pale, felt pain on manipulation of the joints of the extremities, had a palpable spleen 1 fingerbreadth below the costal margin and showed a peculiar color of the skin. Sickling was searched for and found in the peripheral blood stream.

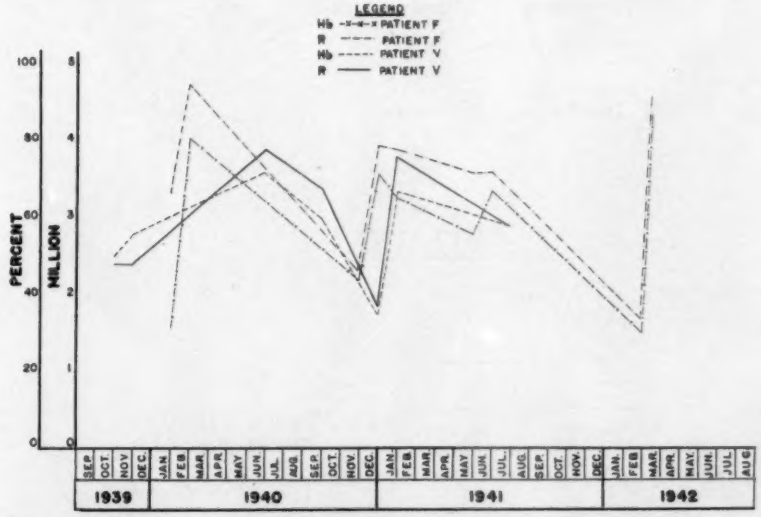

Fig. 1.—Hemoglobin content and red blood cell counts of patients V and F, cases 1 and 2.

Figure 2 presents the familial aspects of the sickling trait.

The fifth admission was on Nov. 8, 1939, for pains in the joints, a cough, pain in the chest and fever. On examination bronchopneumonia was found. There was pronounced sickling of the red cells in the peripheral blood (fig. 3) and in the bone marrow. There was evidence of erythroblastosis in the bone marrow.

The last admission was on Nov. 29, 1940 for pallor and weakness. Examination of the blood gave the following values: hemoglobin content, 35 per cent; red cell count, 1,850,000, and white cell count, 35,200. The spleen was felt 1 fingerbreadth below the costal margin. The bone marrow revealed moderate erythroblastosis.

Case 2.—A white patient, T. F., was observed for the first time when she was 1½ years old. Five weeks prior to her admission to the hospital, she had had

"trench mouth." Six days before this admission she had been treated at home for acute tonsillitis. During this time she had been given sulfanilamide.

On examination she was extremely pale and had enlarged tonsils and cervical nodes. There was no petechiasis. A soft apical murmur was heard over the heart. The spleen felt hard and rubbery and was enlarged to 3 fingerbreadths below the costal margin; the liver was felt 2 fingerbreadths below the costal margin. The

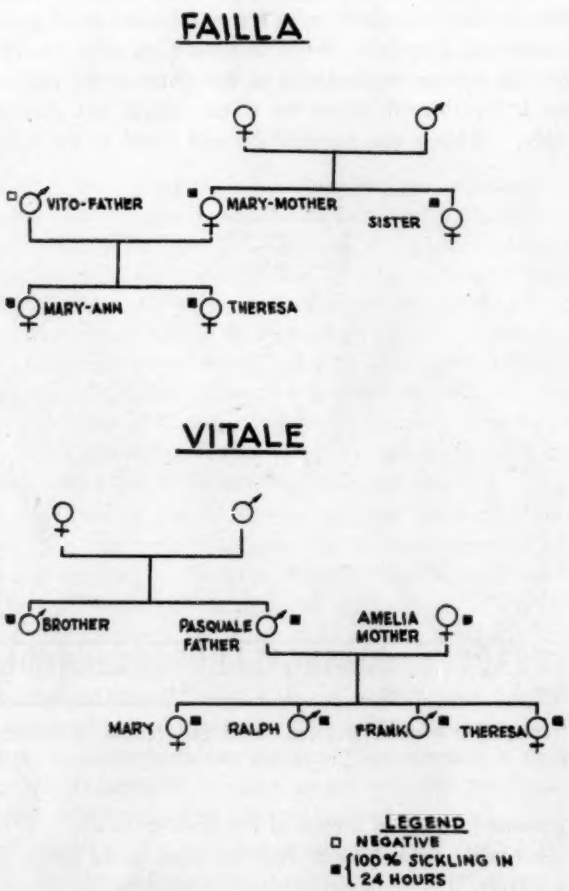

Fig. 2.—Familial occurrence of sickling in the V and F families.

bleeding and clotting times were within normal limits. The icteric index was 11.0. The urine contained no bile, but urobilinogen was present in a dilution of 1:50. Hematologic studies revealed a hemoglobin content of 34 per cent, a red blood cell count of 3,320,000 and a white cell count of 10,000. The platelets were normal in number. Four normoblasts per hundred white cells and stippling were seen. The reticulocyte count was 15 per cent. The result of the fragility test was normal.

Two transfusions, totaling 350 cc., were given. After this, the hemoglobin content was 81 per cent and the red cell count 4,780,000. There was a regression of the spleen, with a gradual, uneventful recovery. The patient was discharged after a stay of eight days. The diagnosis on discharge was hemolytic anemia secondary to sulfanilamide intoxication.

During an interval of ten months, she was seen in the outpatient department from time to time, and increasing jaundice was noted. She was admitted to the hospital

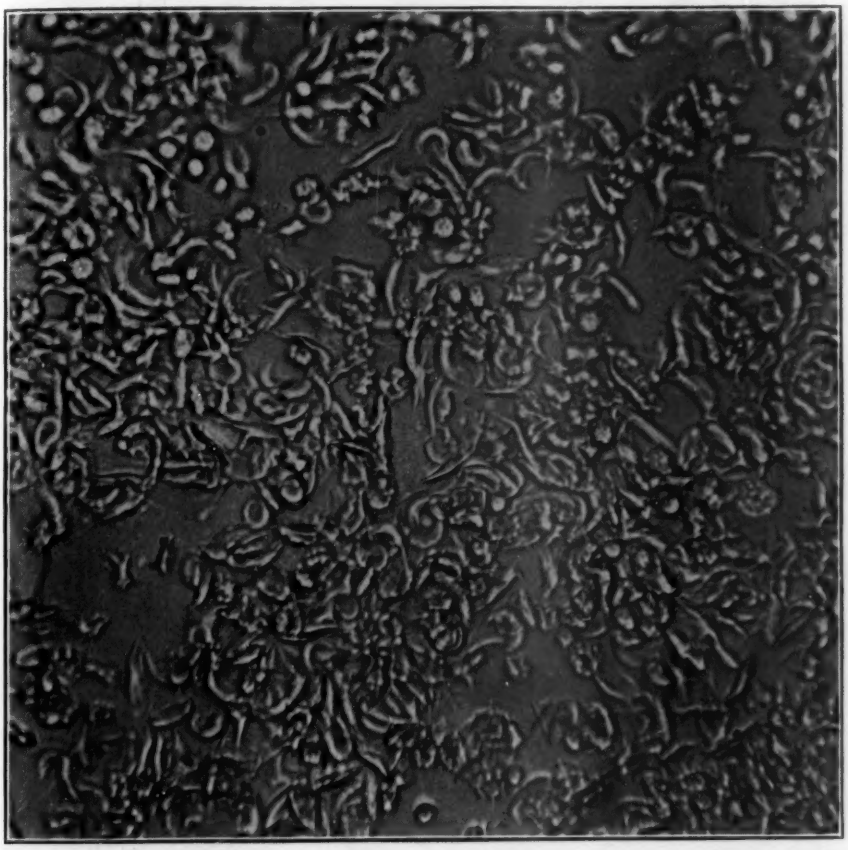

Fig. 3.—Photomicrograph of a moist cover slip preparation, showing sickling of the erythrocytes (patient V).

for the second time on Nov. 9, 1940, with a history of fever, cough, pains in the joints and increasing jaundice.

Physical examination revealed a moderate icterus; the spleen and the liver were palpable 2 fingerbreadths below the costal margin. The fragility test showed an increased resistance. Since sulfanilamide had not been used, a diagnosis of hemolytic icterus was entertained. Hematologic studies showed a hemoglobin content of

44 per cent and a red cell count of 2,300,000. The icteric index was 26.0. Two transfusions of compatible citrated blood were given to combat the anemia, but the hemoglobin content dropped to 29 per cent and red cell count to 1,890,000. This was regarded as a hemolytic crisis, not unusual in some cases of hemolytic icterus. However, investigation of the compatibility of the transfused blood by Dr. A. S. Wiener [1k] revealed that the patient's blood was Rh negative and that he had received transfusions of Rh-positive blood; this accounted for the hemolytic crisis.

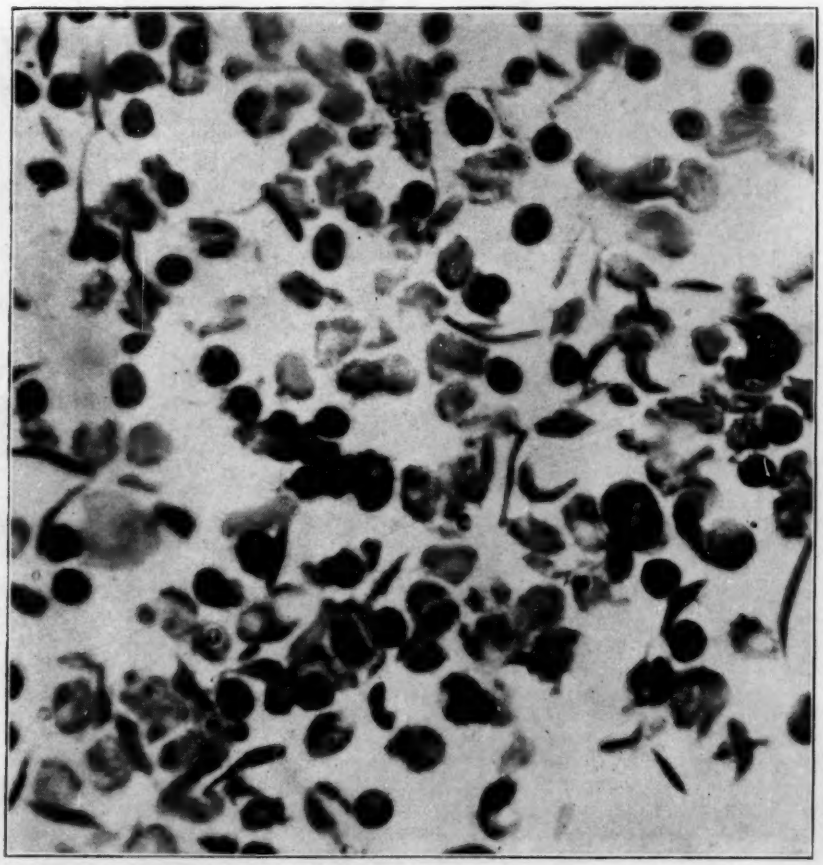

Fig. 4.—Photomicrograph of material obtained by splenic puncture from patient F.

The cause of the original condition, however, remained obscure. A splenic puncture was done routinely and, surprisingly, revealed the presence of sickling (fig. 4). After this, further studies of the bone marrow and peripheral blood also showed the presence of sickling.

COMMENT

The sickling phenomenon was clearly demonstrated in members of the F and V families. The trait was transmitted for three generations.

Patient V (case 1) presented various gradations of sicklemia, from that of sickle cell trait in one admission to a sickle cell crisis in the last admission. Because the patient was white, many opportunities for making the diagnosis were missed. The complicating episodes in the progress of this sickle cell trait were those associated with relative anoxemia (pneumonia, alveolar abscess, pyuria with administration of mandelic acid, etc.).[5]

Case 2 brings out forcibly the difficulty one encounters in differentiating the primary hemolytic disorders from the hemolytic episodes consequent to therapy with sulfonamide compounds. The first thought was to exclude the drug as the cause and then the hemolytic icterus. The former was readily ruled out since there was a recurrence of the hemolytic picture after ten months. During this time no sulfonamide compounds were administered. The latter was ruled out because of persistent normal results of fragility tests. At this point a satisfactory explanation for the hemolytic disorder was still wanting, since for the moment the complicating incompatibility with regard to the Rh factor had been forgotten. A splenic puncture was done, and it revealed an erythroblastosis with marked sickling.

Aspirations of bone marrow in both patients showed a great increase in erythrogenesis associated with a maturative defect of the red blood cells. There were evidences of cell destruction in the peripheral smear (poikilocytosis, microcytosis, polychromatophilia, etc.). These cases demonstrate the fact that search for the sickling phenomenon should be undertaken in all cases of obscure hemolytic disorders, even in white patients, and if possible a splenic puncture should be done in cases in which splenomegaly is present.

SUMMARY AND CONCLUSIONS

Two cases of sickle cell anemia occurring in 2 unrelated white (Italian) families going back three generations are reported.

Splenic puncture is a valuable adjunct in confirming the phenomenon of sickling in obscure cases.

645 Ocean Avenue.

135 Eastern Parkway.

555 Prospect Place.

5. Kracke, R. R.: Diseases of the Blood and Atlas of Hematology, ed. 2, Philadelphia, J. B. Lippincott Company, 1941, p. 327.

NEUROFIBROMATOSIS OF THE COLON, SMALL INTESTINE AND MESENTERY IN A CHILD

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AND
JAMES W. BRUCE, M.D.
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This case is presented as the first to be recorded in the literature of neurofibromatosis of the colon in a child. According to Miller and Frank,[1] there is no uniformity of opinion as to the classification or histogenesis of such tumors. The name neuroma, which is perhaps the oldest one, was used by writers contemporary with von Recklinghausen. Other descriptive names include neurilemmoma, neuronoma, peripheral fibroglioma, fibroblastoma, neurogenic fibroma, neurinoma, peripheral glioma, lemmoma, schwannoma, false neuroma and perineural fibroblastoma.

Weber [2] described the case of a 30 year old man in whom the appendix reached a length of 20 cm. because of a giant growth of this type. In all of its walls was found an overgrowth of nerve webs with large ganglion cells. This same condition was observed in the cecum and in the colon. Rivas Diez [3] described a case of involvement of the cecum in a 50 year old man with von Recklinghausen's disease of the skin. Multiple tumors the size of small nuts had caused an intussusception of the cecum into the transverse colon. Microscopically they were typical neurofibromas. Mosioka [4] reported finding a solitary knob of tissue such as is observed in von Recklinghausen's disease, consisting of deformed nerve tissue, in the wall of the cecum of a man suffering from acute appendicitis. Glenn [5] stated that "in a diligent search of the literature, no histologically proved case of neurogenic fibroma of the large intestine was found." He reported a case of a neurofibroma in the mesenteric portion of the transverse colon in a 25 year old woman. Eerland [6] reported a case in which the condition occurred in a 43 year

From the Department of Pediatrics, University of Louisville School of Medicine.

1. Miller, A. J., and Frank, L. W.: Ann. Surg. **109**:246, 1939.
2. Weber: Arch. f. klin. Chir. **173**:259, 1932.
3. Rivas Diez, B.: Semana méd. **2**:457, 1937.
4. Mosioka, K.: Taiwan Igakkai Zasshi **36**:260, 1937.
5. Glenn, F.: Surgery **6**:703, 1939.
6. Eerland, L. D.: Zentralbl. f. Chir. **67**:724, 1940.

old woman. The cecum had many firm tumors on pedicles. There was a giant-like mucocele of the appendix, 20 cm. in length and 7.5 cm. in diameter. Microscopic sections showed typical neurofibromatosis.

Neurofibromatosis of the mesentery is rare. Macnaughton-Jones [7] cited a case of ganglion neuroma (partly embryonic in structure) of the mesentery. Neurofibromas of the mesentery have also been described by Oberndorfer,[8] Schmincke,[9] Baltisberger [10] and Dudley,[11] and one of the omentum by Biasini.[12]

Neuroma of the appendix is common. Fein, Hanan and Seidler [13] have found it present in 202 appendixes of a series of 600. Sixty-four per cent of these were involved by appendicitis of the obliterative type.

Neurofibromatosis of the small intestine is uncommon. We have found 9 cases, but we are satisfied there are more instances of it in the literature.

The following case is presented because of its rarity and because of its diagnostic interest.

REPORT OF A CASE

A Negro girl was first seen in the pediatric clinic of the Louisville City Hospital on Jan. 22, 1941, when she was 8 years old, complaining of an infection of the upper respiratory tract. At that time there was found an asymptomatic, irregular, nontender, hard, freely movable mass extending from the umbilicus laterally for 12 cm. It was not fixed to the skin and seemed to be a part of the intestine. Other physical conditions and the past history were irrelevant. There was no history of neurofibromatosis, cancer or tuberculosis in the family. At that time no attempt at diagnosis of the tumor mass was made.

She returned to the clinic on October 17 and was admitted to the ward for a diagnosis of the tumor mass. It apparently had not become enlarged and was still asymptomatic. She weighed 50 pounds (22.7 Kg.), was in good health and seemed to be an alert and active child. She had normal bowel movements and normal urinary function. There were no neurofibromas of the skin, and fluoroscopic examination of the skeleton revealed no abnormalities.

Repeated blood counts and urinalyses gave normal results. The reaction to old tuberculin in a dilution of 1:1,000 and the Kahn reaction of the blood were negative. Cultures of a stool and the reaction of a benzidine test for occult blood in the stool were negative. The roentgenogram of the chest showed well healed childhood tuberculosis. The series of roentgenograms of the gastrointestinal tract showed narrowing of the terminal portion of the ileum, which was irregular in

7. Macnaughton-Jones, H.: Proc. Roy. Soc. Med. (Sect. Obst. & Gynaec.) **5**:287, 1912.

8. Oberndorfer: Verhandl. d. deutsch. path. Gesellsch. **18**:148, 1921.

9. Schmincke: Zentralbl. f. allg. Path. u. path. Anat. **33**:17, 1922.

10. Baltisberger: Beitr. z. path. Anat. u. z. allg. Path. 459, 1922.

11. Dudley, G. S.: S. Clin. North America **10**:539, 1930.

12. Biasini, A.: Policlinico (sez. chir.) **45**:535, 1938.

13. Fein, M. J.; Hanan, J. T., and Seidler, V. B.: Am. J. Surg. **39**:27, 1938.

contour and moderately fixed. The cecal tip was irregular, and the whole picture was characteristic of a terminal ileitis. The roentgenogram taken after a barium sulfate enema showed no abnormalities except the conditions in the cecum.

Intravenous pyelograms (fig. 1) showed prompt and satisfactory output of the dye into both renal pelves. There was a congenital anomaly of both kidneys. The anomaly consisted of a bifid pelvis on the left side and on the right a double kidney and a double ureter, which extended down to the level of the fourth

Fig. 1.—Intravenous pyelogram.

lumbar vertebra. At this point there was apparently an obstruction, causing a hydroureter. The ureter below this point presented a normal appearance.

An exploratory laparotomy was done by Dr. Arnold Griswold on December 9 (fig. 2), revealing many large nodular masses having the appearance of tapioca and involving the mesoappendix, the appendix, the mesocolon to the cecum and transverse colon, the cecum, the ascending colon and the mesentery to the terminal 2 feet (60 cm.) of the ileum; there were smaller masses along the aorta. A specimen for biopsy was taken from the cecum and mesoappendix. An ileosigmoidostomy shunting the distal 2 feet of the ileum, cecum and ascending, transverse

and descending colon was done. Five grams of sulfadiazine was dusted into the peritoneal cavity and the wound closed. She made an uneventful convalescence, being discharged on the fifteenth postoperative day.

She was readmitted to the hospital on Jan. 5, 1942, and the operative wound was reopened by Dr. Griswold on January 8. The anastomosis was found to be well healed, but at one point near the anastomosis there was a nodule of apparently encapsulated sulfadiazine about 0.5 cm. in diameter, biopsy of which showed chronic purulent inflammation with foreign body giant cell reaction and crystalline deposits in granulation tissue. There was, however, no excess of adhesions due to sulfadiazine. The distal 2 feet of the ileum and the entire colon were removed with

Fig. 2.—Appendix and tumor masses. Note their size in comparison with the finger and thumb.

all of the involved mesentery. The child was clinically well on the fifth postoperative day and wanted to go home. A subsequent roentgenogram taken after a barium sulfate enema showed a normal functioning anastomosis. She was seen one month postoperatively and had no complaints. She was having two semisolid bowel movements per day and one at night.

Dr. A. J. Miller interpreted the surgical specimen (fig. 3). It consisted of the distal portion of the ileum, approximately 80 cm. in length, the cecum, the ascending colon, the transverse colon, and the descending colon to the junction of the sigmoid flexure. Two loops of the ileum were adherent. Throughout the mesentery were enlarged lymph nodes, the largest of which was about 2 cm. in the longest

diameter. In the mesentery of the ileum at the bowel attachment, there were innumerable tumor masses, of which some were distorted, some were coherent and others extended up on the wall of the bowel. There was a large mass involving the mesentery at the ileocecal junction so as to distort the mesentery of the ileum and cecum in appearance. This mass, measuring 10 by 7 by 6 cm., was similar to the smaller ones in character. It had pushed the ileum down anteriorly and had encroached somewhat on the lumen of the cecum. The appendix was 10 cm. in length and 2.8 cm. in diameter, and at its midpoint it was adherent to the cecum and to the ileum, apparently by tumor growth. In the mesentery of the colon, there were nodules similar to those in the mesentery of the ileum. Some of these masses were elongated and somewhat

Fig. 3.—Surgical specimen of colon, ileum, mesentery and regional tumor masses.

strandlike. In the cecum and in the lower part of the ascending colon, it appeared that the tumor growth did not extend through the wall of the colon, but at the cecum a papillary-like mass approximately 2 by 3 cm. presented into the lumen at the base of the appendix. This was the result of tumor growth extending into the submucosa.

On microscopic examination (fig. 4), multiple sections of the small intestine and colon revealed many of the mucosal glands to be hyperplastic. In many areas of the mucosa and the submucosa, there were recent hemorrhage and necrosis. These were probably due to operative trauma. The intestinal wall was enormously thickened and consisted of whorls and parallel bundles of cells and delicate wavy fibrils. In many areas these cells and fibers appeared teased apart. There was an extensive proliferation of nerve fibers, and a transverse section through these

areas gave the appearance of an amputation neuroma (fig. 5). Sections of the mesenteric tumors showed similar proliferation. Sections of some of the accompanying lymph nodes revealed hyperplasia, but no tumor was found in them. The pathologic interpretation was neurofibromatosis of the colon, cecum, small intestine and mesentery.

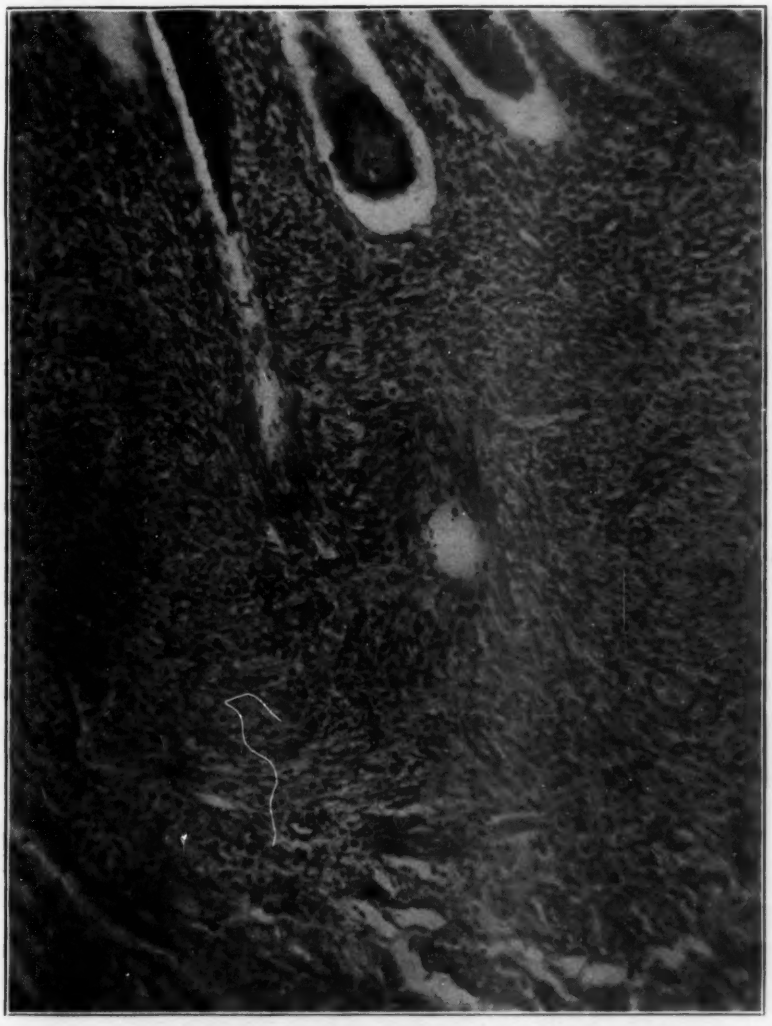

Fig. 4.—Microscopic section from colon (approximately × 80).

The case of this child is similar to the case published by us.[14] Both children were underdeveloped and had asymptomatic masses, found during a routine physical examination. Both had almost the same renal

14. Chalkley, T. S., and Bruce, J. W.: J. Pediat. **20**:632, 1942.

anomalies. However, this child did not have a history of neurofibromatosis in the family, as the other child did.

A large amount of resection was necessary to eradicate all of the tumor, but of course it may well recur. Apparently there is not going to be much detriment to the child's health, since she is regaining her weight well and having only three bowel movements a day.

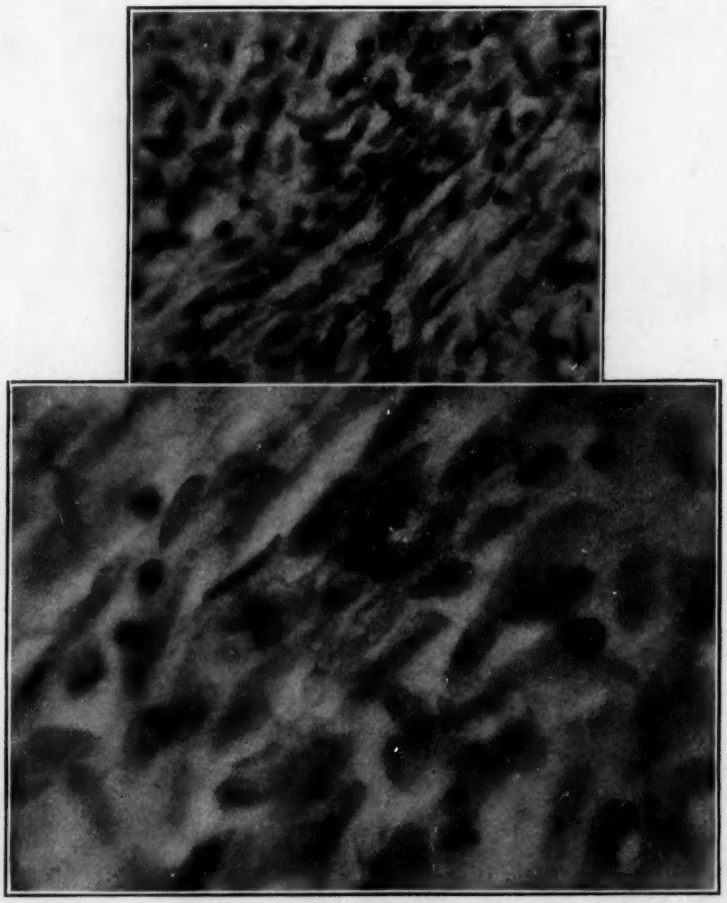

Fig. 5.—Tumor cells (× 225 above; × 450 below).

SUMMARY

A case of neurofibromatosis of the colon, small intestine and mesentery is presented. This is the first case in the literature of a tumor of this sort occurring in the colon in childhood. A complete resection of the colon with the terminal 2 feet (60 cm.) of the ileum was done, and the child made an uneventful recovery.

HERPES ZOSTER IN THE NEWBORN

REPORT OF ITS OCCURRENCE IN A THREE DAY OLD INFANT

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AND

SIDNEY GURIAN, M.D.

NEW YORK

Herpes zoster, a disease frequently encountered in adults, is much less often seen in children and is extremely rare in infancy. Lang,[1] in a review of 10,000 cases observed at the dermatologic clinic of the University of Vienna and a great number of additional cases gathered from the literature, reported in 1938 that the highest figure for incidence in infants was less than 0.07 per cent of all cases of herpes zoster. If patients seen in the first months of life alone are considered, this figure is still lower.

During the course of forty years Comby [2] observed 84 cases of herpes zoster in children. Nine of the patients were in the first two years of life, the youngest an infant of 8 months. Gaehde [3] in 1897 reported a case of herpes zoster in a 3 week old infant of an eclamptic mother. Bonar and Pearsall [4] in a report published in 1932 described a case of herpes zoster appearing in a 4 day old white girl. In reviewing the literature they could find only 2 other cases in which the disease occurred during the newborn period: the case of a 4 day old baby reported in 1889 by Lomer [5] and the questionable case of Kolb [6] reported in 1909. Kolb considered symmetric scars on the face of a newborn baby as due to an intrauterine herpes zoster. In the same years that the article of Bonar and Pearsall appeared, Tausch [7] reported the case of a child born with unilateral herpetic lesions having a segmentary distribution. He also mentioned another case of herpes zoster

From the Department of Pediatrics, New York Medical College, Flower and Fifth Avenue Hospitals, and Metropolitan Hospital (Department of Hospitals).

1. Lang, J.: Arch. f. Dermat. u. Syph. **176**:515, 1938.
2. Comby, J.: Bull. et mém. Soc. méd. d. hôp. de Paris **46**:992, 1922.
3. Gaehde, F.: Deutsche med. Ztg. **101**:1016, 1897.
4. Bonar, B., and Pearsall, C.: Herpes Zoster in Newborn, Am. J. Dis. Child. **44**:398 (Aug.) 1932.
5. Lomer, H.: Centralbl. f. Gynäk. **13**:778, 1889.
6. Kolb, O.: Zentralbl. f. Gynäk. **33**:929, 1909.
7. Tausch, M.: Zentralbl. f. Gynäk. **56**:1629, 1932.

in a 4 day old infant, reported by Bohn [8] in 1869. Since these last reports the only other case of herpes zoster in a newborn infant which has appeared in the literature was that of a 12 day old child mentioned by Katayama [9] in 1938.

REPORT OF A CASE

P. Y., a white girl, was born on Aug. 8, 1941. The mother, who was pregnant for the first time, gave an entirely normal medical history and had not taken any medication prior to the delivery of the child.

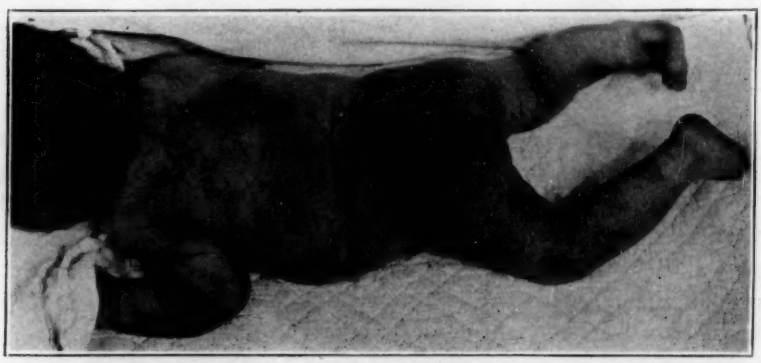

Fig. 1.—Photograph of the newborn girl, showing the vesicles on the right leg.

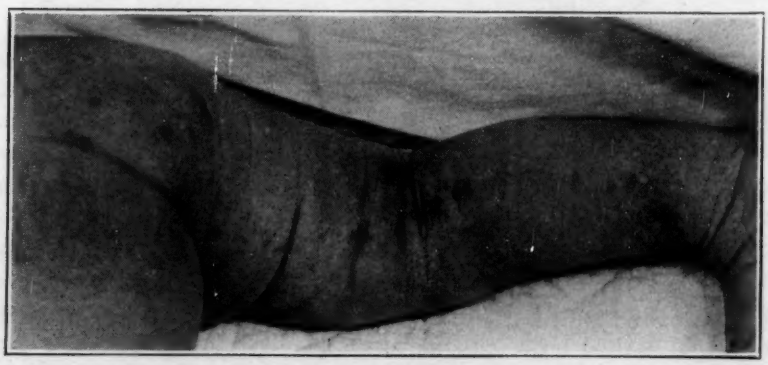

Fig. 2.—The right leg of the infant, showing the vesicles following the course of the sciatic nerve.

The infant was delivered from the left occipitotransverse position with a Kielland forceps. She was in good condition after the delivery and cried spontaneously. A complete examination shortly afterward revealed only a slight abrasion under the right eye and some discoloration of the skin below the left ear.

Three days later (August 11) vesicles appeared on the right lower extremity, following the course of the sciatic nerve from the buttock to the heel. There

8. Bohn, cited by Tausch.[7]

9. Katayama: Jap. J. Dermat. & Urol. **43**:145, 1938.

were typical herpetic lesions on an erythematous base, and a diagnosis of herpes zoster was made. The same day thrush appeared in the baby's mouth.

Roentgenograms of the dorsolumbar region of the spine and the pelvis were normal. The Wassermann reaction was negative. The blood count and smears showed no abnormalities.

The thrush cleared up rapidly with gentian violet therapy, but no treatment was administered for the herpes, because the infant did not appear to be in any discomfort and gained weight regularly. She was discharged on August 28 with some of the lesions still present.

Because of the suggestion, made soon after the appearance of the eruption, that it might be a keratotic linear birthmark which had been overlooked after delivery, the infant was observed at home; by October 1 all the lesions had disappeared completely.

COMMENT

A thorough review of the literature revealed only 5 cases of herpes zoster in the newborn. In 1 of these cases, that of Kolb, the eruption was diagnosed as probably due to an intrauterine herpes zoster because of scarring on the face. Kolb considered infection to be the causative factor, while Bonar and Pearsall assumed a toxic cause in their case.

Trauma and toxins, as far as could be determined, played no part as etiologic factors in the case presented here; hence an infectious causation becomes very likely. Since the incubation time of herpes zoster is from three to fourteen days but may be, according to Pick,[10] only several hours, an intrauterine transmission is as likely as an infection after birth.

The presented case has, in common with the few other cases of herpes zoster reported in infants, the absence of apparent pain or discomfort. However the course differed somewhat from that in other cases in that a longer period (about six weeks) was necessary for complete healing; there was no scarring.

111 East Sixty-First Street (Dr. Freud).

10. Pick, cited in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1928, vol. 7, pt. 1.

Progress in Pediatrics

NUTRITIONAL REQUIREMENTS IN INFANCY AND IN CHILDHOOD

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I. RECOMMENDED DAILY ALLOWANCES

Since the daily allowances for specific nutrients recommended by the National Nutritional Conference of June 1941 represent the con-

Recommended Daily Allowances for Specific Nutrients *

	I	II	III	IV	V	VI	VII	VIII	IX	X
	Calories	Protein, Gm.	Calcium, Gm.	Iron, Mg.	Vitamin D, U.S.P. Units	Vitamin A, U.S.P. Units	Ascorbic Acid, Mg.	Thiamine, Mg.	Riboflavin, Mg.	Niacin (Nicotinic Acid)
Children up to 12 yr.										
Under 1 yr.	100 per Kg.	3-4 per Kg.	1.0	6	400-800	1,500	30	0.4	0.6	4
1- 3 yr.	1,200	40	1.0	7	?	2,000	35	0.6	0.9	6
4- 6 yr.	1,600	50	1.0	8	?	2,500	50	0.8	1.2	8
7- 9 yr.	2,000	60	1.0	10	?	3,500	60	1.0	1.5	10
10-12 yr.	2,500	70	1.2	12	?	4,500	75	1.2	1.8	12
Children over 12 yr.										
Girls: 13-15 yr.	2,800	80	1.3	15	?	5,000	80	1.4	2.0	14
16-20 yr.	2,400	75	1.0	15	?	5,000	80	1.2	1.8	12
Boys: 13-15 yr.	3,200	85	1.4	15	?	5,000	90	1.6	2.4	16
16-20 yr.	3,800	100	1.4	15	?	6,000	100	2.0	3.0	20
Pregnancy (latter half)	2,500	85	1.5	15	400-800	6,000	100	1.8	2.5	18
Lactation	3,000	100	2.0	15	400-800	8,000	150	2.3	3.0	23

* Prepared by the Committee on Foods and Nutrition, National Research Council.

sensus of the leading authorities on nutrition in this country, their consideration provides a convenient means of discussing recent opinion on this subject. The "recommended daily allowances," not "minimal or optimal requirements," are presented in the accompanying table. If one considers the unsatisfactory nature of minimal requirements as dietary standards and the difficulty of establishing optimal requirements, the wisdom of the nomenclature used becomes apparent.

Column I gives the caloric allowances for persons of various ages and women during pregnancy and lactation. The figures are rough

Delivered in part as an address before the Institute of Nutrition, Cincinnati, Oct. 29, 1941.

From the Department of Pediatrics, Harvard Medical School, and the Children's Medical Service, Massachusetts General Hospital.

approximations of total allowances except for infants "under 1 year" of age, for whom the figure is in terms of calories per kilogram of body weight. This figure of 100 calories per kilogram is perhaps low for small infants. The allowances of from 1,200 to 3,800 calories for the other groups appear liberal and have been generally accepted for some time. It is of interest to note that many of these caloric figures derive from the studies of the second half of the nineteenth century, when respiratory calorimetry in the hands of such masters as Liebig, Voit, Rubner and Lusk provided a vast amount of information concerning energy or caloric requirements.

The division of foodstuffs by Liebig about 1860 into proteins, fats and carbohydrates satisfied the concepts used in the study of nutrition for roughly half a century. The impressive advances in the knowledge of nutrition that accrued from such studies led to the belief that their continuation in conjunction with the provision of diets consisting of pure protein, carbohydrate and fat would provide the ultimate standards of optimal nutrition. Thus, instead of the sort of table presented here, a table of recommended allowances in 1900 would have dealt largely with calories, protein, fat and carbohydrate. The quantitative requirements would have been given in detail and with great confidence for each category of food without consideration of possible differences in nutritive quality. Indeed, in spite of the known antiscorbutic property of certain foods, Voit[1] in 1881 suggested that it would be interesting to prove the validity of such allowances by feeding only chemically pure proteins, carbohydrates, fats and inorganic salts, though he apparently felt that experimental confirmation was so certain that the study was hardly worth while. Yet in column II of the table, the protein requirements, as will be mentioned subsequently, are based on distinctly different criteria than obtained in 1900, and no mention is made of fat and carbohydrate. The omission of these factors is not because the old data were wrong, but rather because other things superseded them in importance. The accumulation of most of the knowledge that has wrought this change has occurred during the last twenty years, much of it within the last five years.

In 1906 F. G. Hopkins[2] shattered Voit's illusion by stating that "no animal can live upon a mixture of pure protein, fat and carbohydrate and even when the necessary inorganic material is carefully supplied the animal still cannct flourish." With the recognition of this fact, a new type of nutritional study was begun in the early nineteen hundreds in the laboratories of Hopkins, Hart and Steenbock, Osborne

1. Voit, C.: Die Ernährung, in Hermann, L.: Handbuch der Physiologie, Leipzig, F. C. W. Vogel, 1881, vol. 6, pt. 1.

2. Hopkins, F. G., 1906, cited by Mendel, L. B.: Nutrition: The Chemistry of Life, New Haven, Conn., Yale University Press, 1923.

and Mendel, McCollum, Sherman and others. The essential technic of these experiments was the observation of the growth and development of experimental animals as specific food substances were added to or taken from a standard basic diet. It is well to remember that much of present knowledge of the requirements of all the specific nutrients in the table is based on such experiments on animals and should be applied with due care to human nutrition. As the purification of food substances progressed, these studies demonstrated the essential nature of various factors. Certain amino acids, regardless of their caloric value or nitrogen content, and certain inorganic salts were found to be essential components of cell structure. Other substances, the requirements of which were too small to indicate that they possessed either caloric or structural value, were found to subserve then unknown but essential functions and were called vitamins. During the past few years the enzymatic nature of their role has been revealed with startling rapidity.[3]

Though the figures for protein allowances in the table were established some years ago, it is interesting that the identification of the complete set of amino acids, which was begun by Hopkins and Osborne and Mendel, was completed only as recently as 1935 with Rose's discovery of threonine.[4] With the complete set of amino acids thus at hand, Rose and co-workers[5] in 1937 assembled the evidence which showed that phenylalanine, lysine, leucine, isoleucine, valine, arginine, threonine, methionine, tryptophan and histidine are indispensable to the normal growth of laboratory animals and probably of human beings. Thus it was only two years ago that the way finally was opened for the accurate study of the role played by the various amino acids in the structure and function of specific organs. Since it is not alone the total nitrogen or caloric content of protein that prescribes the protein allowances, but rather the content of essential constituents, such as amino acids, vitamins of the B complex and other indispensable factors, the importance of Rose's work is readily appreciated. If the total nitrogen were the determining factor, the protein allowances could be much smaller. For example, the cow's milk requirement of the formula-fed infant is determined by the demand for specific amino acids, not for total protein or nitrogen. Much of the present tendency to emphasize protein

3. Ball, E. G.: Chemical Reactions of Nicotinic Acid Amide in Vivo, Bull. Johns Hopkins Hosp. **65**:253 (Sept.) 1939. Kalckar, H. M.: The Nature of Energetic Coupling in Biological Syntheses, Chem. Rev. **28**:71 (Feb.) 1941.

4. McCoy, R. H.; Meyer, C. E., and Rose, W. C.: Feeding Experiments with Mixtures of Highly Purified Amino Acids: VIII. Isolation and Identification of a New Essential Amino Acid, J. Biol. Chem. **112**:283, 1935. Meyer, C. E., and Rose, W. C.: The Spatial Configuration of α-Amino-β-Hydroxybutyric Acid, ibid. **115**:721, 1936.

5. Rose, W. C.: Nutritive Significance of Amino Acids, Physiol. Rev. **18**:109 (Jan.) 1938.

allowances springs from the desire to provide the now popular B vitamins. The figures for the protein allowances, column II, agree with those generally used.

In considering the figures of column III, one perhaps should remark that calcium requirements and therefore recommended allowances are affected, among other things, by the amount of vitamin D or ultraviolet rays provided. However, no amount of vitamin D or ultraviolet rays will provide proper calcium retention in the growing child if the daily intake of calcium is below approximately 0.3 Gm. In view of the fact that the allowances in table I include adequate vitamin D, the calcium allowances of from 1.0 to 1.4 Gm. are pretty liberal.

There is no need of specifying phosphorus allowances in the table, because an adequate intake of protein and calcium guarantees an abundance of phosphorus.

The figures for iron, column IV, are the rather widely accepted ones. Actually there are few accurate data applicable to the requirements of children. Considerable evidence suggests that the figures in the table for children under 12 years of age might be somewhat higher than the 6 to 12 mg. listed. The iron stores and state of nutrition are determined not only by the dietary intake but in infancy by the preparturient state of the mother as regards iron nutrition, by the maturity of the infant at birth, and in infancy and childhood by infection. Copper need not be specifically listed, as the allowance is small and is covered by any diet adequate in other respects.

Because the allowances recommended for the remaining six specific nutrients, namely, the vitamins, either are the subject of controversy or are in need of further verification, they should be considered as no more than rough approximations.

There is no quantitative chemical or biologic method of measuring vitamin D that is applicable to studying the nutritional state of a person with regard to vitamin D. Appraisal of vitamin D nutrition is dependent on indirect methods—roentgenograms and determinations of serum calcium, serum inorganic phosphorus, serum phosphatase, growth and calcium balance. With use of these indirect methods, clinical observation has provided fairly reliable information on which to estimate allowances. Yet, there is considerable disagreement on the allowances of vitamin D. The values given in the table represent a compromise. Jeans and co-workers [6] have provided much evidence that 400 U. S. P. units provides an adequate dietary allowance and that such an allowance should be specified for all the age groups shown in the table. Others feel that clinical observations suggest for certain ages and during pregnancy

6. Jeans, P. C., and Stearns, G.: Human Requirement of Vitamin D, J. A. M. A. **111**:703 (Aug. 20) 1938.

and lactation a requirement of as much as 1,200 U. S. P. units. Park [7] has stated that premature infants may need as much as 5,000 to 10,000 U. S. P. units and full term infants from 800 to 1,200 U. S. P. units daily throughout the first year. The figures of 400 to 800 U. S. P. units of vitamin D, as given in column V in the table, for infancy, pregnancy and lactation appear adequate, except for persons with conditions that deserve medical attention and special consideration. In addition, there seems ample evidence [8] that 400 U. S. P. units should be definitely specified throughout the entire period of growth.

The allowances given in column VI for vitamin A might well be put lower if the entire requirement were to be provided by vitamin A. Actually, however, a large portion will be provided by the provitamin, carotene, which is absorbed and utilized about half as effectively as vitamin A. Studies of the vitamin A requirements for the prevention of severe night blindness in a variety of animals suggest that the requirement per kilogram of body weight is almost a constant for many vertebrates and probably for man, the figure being 25 U. S. P. units of vitamin A per kilogram or 45 U. S. P. units in the form of carotene.[9] Studies on the requirements that prevent small changes in dark adaptation, rather than gross night blindness, and permit minimal storage indicate that approximately double these amounts provide adequate allowances.[10] This suggests an allowance of approximately 3,600 U. S. P. units of vitamin A or 6,000 U. S. P. units of carotene for a 70 kilogram man. On this basis the figures given in the table appear reasonable. For example, on the basis of 50 U. S. P. units of vitamin A per kilogram, a liberal allowance during infancy would appear to be 60 times 10 Kg., or 600, U. S. P. units of vitamin A. It is true that premature infants are born with lower supplies of vitamin A in their livers than are full term infants.[11] But this does not necessarily indicate the need of a high allowance. Clausen and McCoord [11c] have examined the livers of older premature infants who had had the usual diets and have always found considerable amounts of vitamin A in their livers.

7. Park, E. A.: Use of Vitamin D Preparations in Prevention and Treatment of Disease, J. A. M. A. **111**:1179 (Sept. 24) 1938.

8. Jeans and Stearns.[6] Park.[7]

9. Guilbert, H. R.; Miller, R. I., and Hughes, E. H.: The Minimum Vitamin A and Carotene Requirement of Cattle, Sheep and Swine, J. Nutrition **13**:543 (May) 1937. Guilbert, H. R.; Howell, C. E., and Hart, G. H.: Minimum Vitamin A and Carotene Requirements of Mammalian Species, ibid. **19**:91 (Jan.) 1940.

10. Booker, L. E.: Chemical Aspects of Riboflavin, J. A. M. A. **110**:1920 (April 2) 1938.

11. (*a*) Toverud, K. U., and Ender, F.: Vitamin A and D Content of Liver of Newborn Infants, Acta pædiat. **18**:174, 1935. (*b*) Ellison, J. B., and Moore, T.: The Vitamin-A Reserves of the Human Infant and Child in Health and Disease, J. Soc. Chem. Industry **55**:236 (March 20) 1936. (*c*) Clausen, S. W., and McCoord, A. B.: Personal communication to the author.

The perfection of methods for determining carotene and vitamin A [12] in plasma and tissue should soon result in providing more information. It is generally agreed that some of the conclusions drawn from the early biophotometric studies of vitamin A deficiency included errors which led to erroneous conclusions. In using dark adaptation as an index of vitamin A nutrition, it seems advisable to follow Wald's [13] recommendation that poor adaptation should be interpreted as due to dietary deficiency of vitamin A only after it has been demonstrated that the ingestion of vitamin A results in improvement. Without such a check too many other factors may be involved. Kruse [14] has reported that early conjunctival xerosis characteristic of vitamin A deficiency, which is not visible grossly, can be detected by slit lamp examination. His studies suggest that such biomicroscopic examination provides a method of detecting early avitaminosis A and of distinguishing the xerosis of vitamin A deficiency from the corneal lesion of riboflavin deficiency.[15] However, Berliner has questioned the validity of Kruse's interpretations of the biomicroscopic observations, because the spots are not associated with epithelial metaplasia.[16]

Summarizing for vitamins A and D, the allowances in the table, columns V and VI, seem liberal and reasonable. This being so, it is interesting to note that most of the popular vitamin pills contain 10,000 U. S. P. units of vitamin A and 1,000 units of vitamin D, amounts which in a dietary or daily allowance sense are excessive and entail useless expense. Steps have recently been taken by the appropriate federal authorities to limit the content of such pills to the allowances specified in the table.

In considering the allowances of ascorbic acid, column VII, it is interesting to compare them with the 5 to 10 mg. of ascorbic acid recommended for artificially fed infants by the Technical Commission

12. (*a*) Clausen, S. W., and McCoord, A. B.: Carotinoids and Vitamin A of Blood, J. Pediat. **13**:635 (Nov.) 1938. (*b*) Dann, W. J., and Evelyn, K. A.: The Determination of Vitamin A with the Photoelectric Colorimeter, Biochem. J. **32**: 1008, 1938. (c) May, C. D.; Blackfan, K. D.; McCreary, J. F., and Allen, F. H., Jr.: Clinical Studies of Vitamin A in Infants and in Children, Am. J. Dis. Child. **59**:1167 (June) 1940.

13. Steven, D., and Wald, G.: Vitamin A Deficiency: A Field Study in Newfoundland and Labrador, J. Nutrition **21**:461 (May) 1941.

14. Kruse, H. D.: Ocular Manifestations of Avitaminosis A, with Especial Consideration of Detection of Early Changes by Biomicroscopy, Pub. Health Rep. **56**:1301 (June 27) 1941; Milbank Memorial Fund Quart. **19**:207, 1941.

15. Sydenstricker, V. P.; Sebrell, W. H.; Cleckley, H. M., and Kruse, H. D.: Ocular Manifestations of Ariboflavinosis: Progress Note, J. A. M. A. **114**:2437 (June 22) 1940.

16. Berliner, M. L.: Regarding the Early Detection of Avitaminosis A by Gross or Biomicroscopic Examination of the Conjunctiva, Am. J. Ophth. **25**:302 (March) 1942.

on Nutrition of the League of Nations in 1938. According to the evidence now available, such an allowance is inadequate. The figures given in column VII of the table seem reasonable until the allowances for girls and boys and pregnancy and lactation are reached, the figures for which range from 80 to 150 mg. These allowances may be high. Such high values are deduced from experiments which have determined what might be called the physiologically maximal rather than the physiologically desirable intake. For example, Ralli and co-workers [17] determined the amount of ascorbic acid that would maintain the plasma concentration at the approximate renal threshold level of 1.4 mg. per hundred cubic centimeters without resulting in a sharp increase in urinary excretion and thus excessive and useless loss. For the maintenance of such a vitamin C nutritional state, daily intakes of 100 mg. of ascorbic acid were required. But there is little evidence suggesting that such intakes or such high plasma levels are particularly beneficial. For all any one knows they may represent useless extravagance. Holmes, Cullen and Nelson,[18] Snelling,[19] Kajdi, Light and Kajdi,[20] Mindlin [21] and others have discussed the unreliability of single plasma ascorbic acid concentrations as indexes of vitamin C intake or as far as could be determined of vitamin C nutrition. Indeed, there seems little to support the oft encountered statement that fasting plasma levels of 0.6 mg. per hundred cubic centimeters or less reflect deficiency. Mindlin [21] has shown the rapidity with which the plasma ascorbic acid level of infants falls in the absence of the ingestion of ascorbic acid. Though this may be interpreted as an indication of the need for ascorbic acid early in life, there is as yet no evidence that such transient drops in plasma concentration indicate harmful deficiency. Levine and co-workers [22] have reported an abnormal excretion of tyrosine and phenylalanine in the urine of premature babies, which is corrected by the giving of ascorbic acid. More recent work by Dann [23] in his laboratory

17. Ralli, E. P., and Sherry, S.: Adult Scurvy and Metabolism of Vitamin C, Medicine **20**:251 (Sept.) 1941.

18. Holmes, F. E.; Cullen, G. E., and Nelson, W. E.: Levels of Ascorbic Acid in Blood Plasma of Apparently Healthy Children, J. Pediat. **18**:300 (March) 1941.

19. Snelling, C. E.: Plasma Ascorbic Acid of Infants and Children, J. Pediat. **15**:824 (Dec.) 1939.

20. Kajdi, L.; Light, J., and Kajdi, C.: Test for Determination of Vitamin C Storage: Vitamin C Index, J. Pediat. **15**:197 (Aug.) 1939.

21. Mindlin, R. L.: Relation Between Plasma Ascorbic Acid Concentration and Diet in Newborn Infant, J. Pediat. **13**:309 (Sept.) 1938; Variations in Concentration of Ascorbic Acid in Plasma of Newborn Infant, ibid. **16**:275 (March) 1940.

22. Levine, S. Z.; Gordon, H. H., and Marples, E.: Defect in Metabolism of Tyrosine and Phenylalanine in Premature Infants: Spontaneous Occurrence and Eradication by Vitamin C, J. Clin. Investigation **20**:209 (March) 1941.

23. Dann, M.: The Influence of Diet on the Ascorbic Acid Requirement of Premature Infants, J. Clin. Investigation **21**:139 (March) 1942.

demonstrated the same abnormal excretion by full term infants fed cow's milk formulas. Such work may lead to new criteria of appraising the significance of plasma levels and of estimating requirements for the newborn. Turning to older age groups, probably 50 per cent of so-called well fed and healthy people have fasting plasma ascorbic acid concentrations below 0.6 mg. per hundred cubic centimeters. This may mean that they are not consuming what may be called an optimal intake, but it appears improbable that it means that they are suffering from deficiency. Conclusions that at present may be drawn from fasting plasma ascorbic acid concentrations are the following: (1) Fasting plasma or serum ascorbic acid concentrations above 0.6 mg. per hundred cubic centimeters suggest a satisfactory state of vitamin C nutrition; (2) concentrations between 0.6 and 0.3 mg., though often varying with intake of ascorbic acid, are not reliable indexes of vitamin C nutrition; (3) levels below 0.3 mg. suggest a deficiency in terms of optimal nutrition but of as yet ill defined physiologic significance, and (4) a plasma level of 0 is indicative of vitamin C deficiency but, though almost always present in scurvy, is not diagnostic of scurvy. So also a low serum phosphatase level is consistent with, but not diagnostic of, scurvy.[24] On the other hand, absence of ascorbic acid from the "buffy layer" of centrifuged oxalated or citrated whole blood, i. e., the platelets and white blood cells, is indicative of scurvy or severe deficiency.[25]

The last three columns, VIII, IX and X, present the allowances for thiamine, riboflavin and niacin (nicotinic acid). The quantitative methods of determining these vitamins in blood and urine and the clinical studies, though excellent, are so few or so recent that a detailed discussion of the correctness of their allowances during infancy and childhood is not warranted. With the present state of knowledge one is more concerned with including a complete set of these essential factors than with quantitative recommendations for individual factors. From the data available the allowances given in the table seem adequate and reasonable, with the possible reservation that the allowances for riboflavin may be high. The recommendation of specific allowances for pantothenic acid, pyridoxine and other factors of the vitamin B complex should be deferred until more information is available. From the table it is seen that the allowances for thiamine and riboflavin are of the order of magnitude of

24. Schwachman, H.: Serum Phosphatase in Infantile Scurvy, J. Pediat. **19**:38 (July) 1941. Talbot, N.; Hoeffel, G.; Schwachman, H., and Tuohy, E. L.: Serum Phosphatase as Aid in Diagnosis of Cretinism and Juvenile Hypothyroidism, Am. J. Dis. Child. **62**:273 (Aug.) 1941.

25. (*a*) Butler, A. M., and Cushman, M.: Distribution of Ascorbic Acid in Blood and Its Nutritional Significance, J. Clin. Investigation **19**:459 (May) 1940. (*b*) Crandon, J. H.; Lund, C. C., and Dill, D. B.: Experimental Human Scurvy, New England J. Med. **223**:353 (Sept. 5) 1940. (*c*) Ralli and Sherry.[17]

1 mg. and that for niacin 10 mg. If, as seems to be indicated by much of the evidence now at hand, the therapeutic dose is some ten times the daily requirement, one must think about providing 5 to 10 mg. doses of thiamine and riboflavin and 50 to 100 mg. doses of niacin to deficient persons according to their age and size. In attempting to do so one turns to the available commercial concentrates and finds amounts of the three B factors given in the table of roughly the following orders of magnitude:

B Complex Concentrates for Oral Administration Contain per 4 Cc.

Thiamine hydrochloride	0.4 — 10 mg.
Riboflavin	0.08 — 2 mg.
Niacin	1.0 — 40 mg.

B Complex Concentrates for Parenteral Administration Contain per Cubic Centimeter

Thiamine hydrochloride	approx. 3 mg.
Riboflavin	approx. 0.5 mg.
Niacin	approx. 10 mg.

Thus, there is wide variation in the concentrations of different preparations, and relatively large doses of most are required.

If one turns to the capsules or perles that may be used for older children and adults, one finds that most of them contain approximately:

Thiamine hydrochloride	0.5 — 1 mg.
Riboflavin	0.1 — 1 mg.
Niacin	2.0 — 10 mg.

Hence, perhaps 5 capsules a day may be required for a therapeutically effective dose.

Finally, the content of powdered brewers' yeast per ounce runs from 1 to 4 mg. of thiamine hydrochloride and from 1 to 3 mg. of riboflavin. Several ounces a day, therefore, is needed for effective therapy.

Thus, adequate therapy for deficiencies of vitamin B may require the use of crystalline products. But with the present limitations to knowledge, not all the essential so-called B factors are available in crystalline form; hence one must use therapeutically such crude complexes as are at hand. These concentrates are mentioned only in terms of medication for the deficient patient. They are not required by persons ingesting diversified diets.

II. PRESCRIPTION OF DIETS FOR NORMAL INFANTS AND CHILDREN

The provision of the recommended allowances in the daily diet of infants and children can be accomplished rather simply. This simplicity of dietary prescription holds true for all age groups except the aged.

For this group, for whom ingestion of large diets is contraindicated, the use of concentrates of specific nutrients seems desirable.

A few years ago books were written on the formula feeding of normal infants. Today hours are sometimes spent in lecturing about it. It appears that the prescription of diets for normal infants may be outlined pretty completely in a few paragraphs, as follows:

A year ago it was common practice to prescribe no fluid or food during the first twelve to twenty-four hours. Recent observations of the hypoprothrombinemia which may occur following birth and persist for the first four days of life [26] suggest the desirability of giving orally in physiologic solution of sodium chloride 0.5 mg. of vitamin K or its synthetic equivalent within twelve hours of birth and repeating this daily for four days, unless vitamin K has been given the mother just prior to or during labor. This applies to both breast-fed and formula-fed infants. Good obstetric practice today should include the administration of several milligrams of vitamin K or a synthetic equivalent to the mother during the four hours preceding delivery.

If the mother has ingested a diet that provides the recommended daily allowances for pregnancy and lactation and the infant in nursing receives normal amounts of breast milk, this milk will provide the nutri-

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26. Brinkhous, K. M.; Smith, H. P., and Warner, E. D.: Plasma Prothrombin Level in Normal Infancy and in Hemorrhagic Disease of Newborn, Am. J. M. Sc. **193**:475 (April) 1937. Waddell, W. W., Jr., and Guerry, Du P., III: Effect of Vitamin K on Clotting Time of Prothrombin and Blood, with Special Reference to Unnnatural Bleeding of Newly Born, J. A. M. A. **112**:2259 (June 3) 1939; Role of Vitamin K in Etiology, Prevention, and Treatment of Hemorrhage in Newborn Infant, J. Pediat. **15**:802 (Dec.) 1939. Lawson, R. B.: Treatment of Hypoprothrombinemia (Hemorrhagic Disease) of Newborn Infant, ibid. **18**:224 (Feb.) 1941. Bruchsaler, F. S.: Vitamin K and Prenatal and Postnatal Prevention of Hemorrhagic Disease in Newborn Infants, ibid. **18**:317 (March) 1941. Kato, K., and Poncher, H. G.: Prothrombin in Blood of Newborn Mature and Immature Infants as Determined by Micro Prothrombin Test, J. A. M. A. **114**:749 (March 2) 1940. Astrowe, P. S.; Palmerton, E. S.; Lea, A., and Henderson, V.: Clinical Studies with Vitamin K in Newborn Infants, J. Pediat. **18**:507 (April) 1941. Macpherson, A. I. S.: Treatment of Haemorrhagic Disease of Newborn, Brit. M. J. **2**:433 (Sept. 27) 1941. Hellman, L. M., and Shettles, L. B.: Factors Influencing Plasma Prothrombin in Newborn Infant: Prematurity and Vitamin K, Bull. Johns Hopkins Hosp. **65**:138 (July) 1939. Shettles, L. B.; Delfs, E., and Hellman, L. M.: Factors Influencing Plasma Prothrombin in Newborn Infant: Antepartum and Neonatal Ingestion of Vitamin K Concentrate, ibid. **65**:419 (Nov.) 1939. Maumenee, A. E.; Hellman, L. M., and Shettles, L. B.: Factors Influencing Plasma Prothrombin in Newborn Infant: Effect of Antenatal Administration of Vitamin K on Incidence of Retinal Hemorrhage in Newborn, ibid. **68**:158 (Feb.) 1941. Bohlender, G. P.; Rosenbaum, W. M., and Sage, E. C.: Antepartum Use of Vitamin K in Prevention of Prothrombin Deficiency in Newborn, J. A. M. A. **116**:1763 (April 19) 1941. Beck, A. C.; Taylor, E. S., and Colburn, R. F.: Vitamin K Administered to Mother During Labor as Prophylaxis Against Hemorrhage in Newborn Infant, Am. J. Obst. & Gynec. **41**:765 (May) 1941.

tional requirements for the first four months of life, with the possible exception of vitamin D. Some evidence suggests that vitamin D will be adequate if the mother's supply of the vitamin is adequate. Until the point is clarified, the addition after the first week of 3 or 4 drops per day of some fish oil concentrate appears advisable. At 2 months of age the addition of an ounce (30 cc.) of orange juice diluted with an equal amount of water may be given, not so much to augment the ascorbic acid requirement as to familiarize the baby with a new taste and provide fluid. At 4 months of age the infant's stores of iron begin to be depleted, and the addition of iron-containing food is desirable. Thus, at this age it is wise to omit one breast feeding per day and substitute a cow's milk formula plus some iron-containing food, such as properly milled grain or egg yolk. Weaning should be complete at 6 months. From then on the diet is similar to that of the cow's milk–fed baby at a similar age.

For the newborn child that is to be reared on cow's milk, a formula of equal parts of boiled cow's milk and water plus added sugar to a concentration of about 4 per cent provides a satisfactory formula during the first week. No food is given the first day unless vitamin K is indicated because the mother has received none prior to or during labor. Two ounces (60 cc.) of this formula is given twice on the second day, four times on the third day and thereafter during the first week at four hour intervals six times daily. Vitamin C is provided as 25 mg. of ascorbic acid beginning the second day and is continued daily thereafter until the baby is old enough to ingest 3 ounces (90 cc.) of orange juice daily. A few years ago it was common practice not to prescribe any of the vitamins until the child was 2 or 3 months of age. Today the evidence provided by such work as that already mentioned of Mindlin [21] and Levine [22] suggests that vitamin C should be provided the infant shortly after birth. Similarly, the limited amount of calcium and phosphorus that can be provided to the very young infant and the requirement for skeletal growth suggest the wisdom of providing approximately 400 U. S. P. units of vitamin D to all infants as soon as practical. The poor skeletal mineralization of premature infants during the first six months of life suggests a rather narrow margin of adequate calcification and the need of vitamin D for all infants. Thus today one does not hesitate to state that vitamin C should be provided within the first few days of life and vitamin D within the first week. If a fish liver oil concentrate is specified as the source of vitamin D, more than adequate vitamin A will be assured. As yet too little is known about the infant's nutritional state as regards the vitamins of the B complex to justify any opinion concerning the need of augmenting the normal infant's intake of these factors. Milk is a good source of riboflavin, a fair source of thiamine, and a questionable source of niacin—questionable because, while milk

has been found to contain the pellagra-preventive factor in appreciable amounts,[27] chemists report only 1 mg. of niacin per quart of milk.

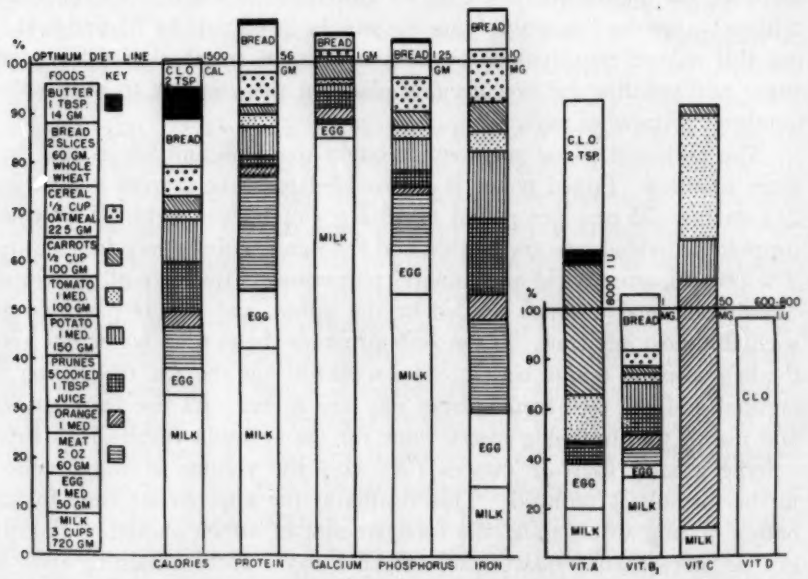
At the beginning of the second week, an adjustable formula is substituted for the one prescribed during the first week. The prescription of this formula is very simple. One third of the total caloric requirement is provided by added sugar. The other two thirds of the caloric requirement is provided by milk. Assuming a caloric requirement of 55 calories per pound, this means for an 8 pound infant $8 \times 55 \times \frac{1}{3}$, or approximately 150 calories of sugar, or about 1¼ ounces (35 Gm.). Because cow's milk has 20 calories per ounce (30 cc.) the milk for an 8 pound infant is $8 \times 55 \times \frac{2}{3} \times \frac{1}{20}$, or 15 ounces (450 cc.), which is just one tenth of the figure for the calories provided as sugar. So the only arithmetic involved is multiplying the weight in pounds by 55 and dividing this caloric requirement by 3 to obtain the number of calories of sugar and pointing off one decimal place on this number to obtain the number of ounces of milk.

The milk and added sugar are brought to a boil and let simmer for three minutes. Boiled water is then added to make a total volume of 2½ ounces (75 cc.) per pound (0.45 Kg.) of body weight. This total formula is divided into six bottles, and the infant is fed every four hours. The protein, amino acid and mineral requirements thus are all provided. Some additional water is needed by the infant, and this is provided as such at almost any time. It not only provides the needed water but gets the baby used to taking water. At 2 weeks of age the 2 a. m. feeding is omitted and but five feedings per day are given. As the baby grows and use of the foregoing instructions for the formula results in a total volume greater than 32 ounces (960 cc.) the volume of water added to the formula is reduced. This results at the appropriate time in the baby's getting whole milk, the total amount of which should ordinarily not be more than 1 quart (960 cc.) per day. Iron-containing food is added to the diet as stated for the breast-fed infant. Thus, at 4 months properly milled and cooked grain is added, and shortly thereafter, hard-boiled egg yolk. At this time the 10 p. m. feeding is omitted; so the infant is on four feedings per day. Next, strained vegetables and fruit are added, and by 7 months, finely shredded meat. By 12 months the diet is fairly diversified, and by 18 months the child is on three meals a day.

27. Goldberger, J., and Tanner, W. F.: Treatment and Prevention of Pellagra: Experiments Showing Value of Fresh Meat and of Milk, Therapeutic Failure of Gelatin, and Preventive Failure of Butter and of Cod-Liver Oil, Pub. Health Rep. **39**:87 (Jan. 18) 1924; Pellagra-Preventive Action of Dried Beans, Casein, Dried Milk, and Brewers' Yeast, with a Consideration of Essential Preventive Factors Involved, ibid. **40**:54 (Jan. 9) 1925. Wheeler, G. A., and Sebrell, W. H.: The Blacktongue (Canine Pellagra) Preventive Value of Fifteen Foodstuffs, in National Institute of Health Bulletin 162, United States Treasury Department, Public Health Service, 1933, p. 1.

Relatively simple instructions cover the dietary needs of later childhood. The child's own appetite is the best guide for the amounts that should be eaten. Specifying the amounts and urging food is the surest way to ruin the appetite.

The chart graphically presents the picture of the nutritional adequacy of a simple diet for the normal preschool child. The foods composing a sample day's diet are given in household measures in the left hand column. Proceeding from left to right, the next columns give the calories, grams of protein, calcium and phosphorus and milligrams of iron provided by this diet. The ordinate scale on the left gives the percentage of the optimum allowance. The numerical value of the recom-



Nucleus for the diet of a normal preschool child. (Adapted by permission from a chart prepared by Bertha Shapley Burke, Department of Child Hygiene, School of Public Health, Harvard University.)

mended daily allowances for total calories and specific nutrients are given at the top of each column on the 100 per cent, or optimum, diet line. Each column is then divided as designated by written word or cross hatching corresponding with the key for each ingredient of the diet in the left hand column, so that the percentage of the total allowance in each column derived from each dietary ingredient is readily estimated. The four columns at the right of the chart with the smaller ordinate scale give in a similar manner the amounts of vitamins A, B_1, C and D provided by this diet. The data presented show how adequately a relatively simple and common dietary fulfils the recommended allowances.

The amount of protein, phosphorus, iron and vitamin B_1 provided by the whole wheat bread and cereal is perhaps worthy of comment and would be much smaller if ordinary refined grain were ingested. The amounts of iron provided by both prunes and potato are appreciable. The greater portion of the vitamin A provided by the foods other than cod liver oil comes from the two vegetables carrots and tomatoes. Because little vitamin C is provided from this diet except that supplied by the orange and tomato, the importance of including a food rich in vitamin C is apparent. It is seen that no significant amount of vitamin D is provided by any of the dietary ingredients unless cod liver oil or some concentrate of vitamin D is added. If the substance added to cover the allowance of vitamin D is a fish liver oil, the amount of vitamin A is greatly augmented. It is also of interest that the inclusion of 4 cups of milk in the diet instead of 3 results in a less satisfactorily balanced diet.

The time of starting the administration of vitamins having been discussed, the question arises as to when special care concerning their specific provision should be stopped. The answer is clear. With the possible exception of vitamin D, their provision must be considered throughout life. This, of course, does not mean that they need be given in the form of concentrates, but rather that the daily food should provide the recommended allowances. Vitamin D, which, as noted in chart 1, does not occur to any significant extent in natural foods, probably serves little purpose after growth is complete, except during pregnancy and lactation. Available data, however, indicate that the equivalent of 400 U. S. P. units of vitamin D daily should be provided throughout infancy, childhood, adolescence, pregnancy and lactation.

Thus, the theoretic provision of a good diet is really relatively simple. If diets similar to those outlined are given in infancy and childhood, then a nutritional disturbance usually means that there is something wrong with the infant or child, not with the diet. Not infrequently it means that something is wrong with the parents. But the point that deserves emphasis is that a nutritional disturbance indicates examining the child, not just shifting the diet. This simplicity of dietary prescription pertains to feeding the average child and must be clearly differentiated from the task of detecting the ailment of and prescribing the diet for the abnormal child. Also beyond the realm of the subject here concerned lie the practical difficulties that the average person encounters in obtaining the diet prescribed by the physician. This, of course, involves other than the purely physiologic aspects of nutrition and brings in problems beyond the ken of physicians. Here one encounters problems of dietary customs and ignorance, which must be solved by educating the public to want to consume and know how to prepare a good diet.

And there are the problems dependent on economic want and faulty marketing and distribution, which economists and sociologists are wrestling with but probably will not solve in the near future. Yet it appears that much might be accomplished toward solving these aspects of our nutritional problems, if thought and action were concentrated on a few questions. For example:

1. How can the producer and consumer be educated to utilize for human nutrition the 50,000,000,000 pounds of skimmed milk thrown away annually in this country, another 50,000,000,000 pounds being used for animal feedings?

2. How can the public be educated to cook food so that excessive loss of its nutritional value is prevented?

3. How can grain be properly milled so that overrefinement does not spoil its nutrient value?

4. How can the cost to the public of concentrates of fish liver oil be reduced?

But these are not matters with which physicians should be concerned. For there remains specifically for them an aspect of nutrition that is both fascinating and full of promise, which is considered in the third section of this review.

III. THE EFFECT OF DISEASE ON NUTRITION AND OF NUTRITION ON DISEASE

The lack of suitable clinical methods of detecting mild deficiencies has until recently limited the dependability of observations on this aspect of nutrition.[28] However, within the last few years new methods of assay have provided information indicating that any change in the diet to conform to or occasioned by some particular physical limitation necessitates a complete dietary check-up to be sure that all the nutritional needs are fully covered. Attention has been directed to the possibility and surgical importance of ascorbic acid deficiency resulting from illness or from the strict dietary regimens prescribed in the treatment of gastric or duodenal ulcers.[29] The relative protein starvation,

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28. Youmans, J. B.: Influence of Vitamin Deficiencies on Other Diseases, Ann. Int. Med. **13**:980 (Dec.) 1939.

29. Harris, L. J.; Abbasy, M. A.; Yudkin, J., and Kelly, S.: Vitamins in Human Nutrition: Vitamin C Reserves of Subjects of Voluntary Hospital Class, Lancet **1**:1488 (June 27) 1936. Archer, H. E., and Graham, G.: Subscurvy State in Relation to Gastric and Duodenal Ulcer, Lancet **2**:364 (Aug. 15) 1936. Lanman, T. H., and Ingalls, T. H.: Vitamin C Deficiency and Wound Healing: Experimental and Clinical Study, Ann. Surg. **105**:616 (April) 1937. Hunt, A. H.: Role of Vitamin C in Wound Healing, Brit. J. Surg. **28**:436 (Jan.) 1941. Ludden,

low serum protein levels and tendency to edema and poor healing of wounds in many patients demanding surgical treatment are recognized and corrected.[30] The increased need of vitamin K in hepatic disease has been demonstrated.[31] The dietary treatment of acute hepatitis and chronic cirrhosis of the liver by a high carbohydrate intake [32] has been effectively supplemented.[33] Von Glahn and Flinn [33a] have prevented

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J. B.; Flexner, J., and Wright, I. S.: Studies on Ascorbic Acid Deficiency in Gastric Diseases: Incidence, Diagnosis and Treatment, Am. J. Digest. Dis. **8**:249 (July) 1941. Bartlett, M. K.; Jones, C. M., and Ryan, A. E.: Vitamin C and Wound Healing: II. Ascorbic Acid Content and Tensile Strength of Healing Wounds in Human Beings, New England J. Med. **226**:474 (March 19) 1942. Portnoy, B., and Wilkinson, J. F.: Vitamin C Deficiency in Peptic Ulceration and Haematemesis, Brit. M. J. **1**:554 (March 12) 1938. Field, H.; Robinson, W. D., and Melnick, D.: Vitamins in Peptic Ulcer, Ann. Int. Med. **14**:588 (Oct.) 1940. Crandon, Lund and Dill.[25b]

30. Jones, C. M.; Easton, F. B., and White, J. C.: Experimental Postoperative Edema, Arch. Int. Med. **53**:649 (May) 1934. Mecray, P. M., Jr.; Barden, R. P., and Ravdin, I. S.: Nutritional Edema: Its Effect on Gastric Emptying Time Before and After Gastric Operations, Surgery **1**:53 (Jan.) 1937. Ravdin, I. S.; Stengel, A., Jr., and Prushankin, M.: Control of Hypoproteinemia in Surgical Patients, J. A. M. A. **114**:107 (Jan. 13) 1940. Rhoads, J. E.; Fliegelman, M. T., and Panzer, L. M.: The Mechanism of Delayed Wound Healing in Hypoproteinemia, ibid. **118**:21 (Jan. 3) 1942.

31. Smith, H. P.; Warner, E. D., and Brinkhous, K. M.: Prothrombin Deficiency and Bleeding Tendency in Liver Injury (Chloroform Intoxication), J. Exper. Med. **66**:801 (Dec.) 1937. Butt, H. R.; Snell, A. M., and Osterberg, A. E.: Preoperative and Postoperative Administration of Vitamin K to Patients Having Jaundice, J. A. M. A. **113**:383 (July 29) 1939. Stewart, J. D., and Rourke, G. M.: Control of Prothrombin Deficiency in Obstructive Jaundice by Use of Vitamin K, ibid. **113**:2223 (Dec. 16) 1939. Pohle, F. J., and Stewart, J. K.: Observations on Plasma Prothrombin and Effects of Vitamin K in Patients with Liver or Biliary Tract Disease, J. Clin. Investigation **19**:365 (March) 1940.

32. Althausen, T. L.: Dextrose Therapy in Diseases of Liver, J. A. M. A. **100**:1163 (April 15) 1933. Jones, C. M.: Treatment of Acute Hepatic Insufficiency and Its Relation to Prognosis, Am. J. Digest. Dis. & Nutrition **3**:624 (Nov.) 1936. Ravdin, I. S.; Rhoads, J. E.; Frazier, W. D., and Ulin, A. W.: Effect of Recent Advances in Biliary Physiology on Mortality Following Operation for Common Duct Obstruction, Surgery **3**:805 (June) 1938.

33. (*a*) Von Glahn, W. C., and Flinn, F. B.: Effect of Yeast on Incidence of Cirrhosis Produced by Lead Arsenate, Am. J. Path. **15**:771 (Nov.) 1939. (*b*) Patek, A. J., Jr., and Post, J.: Treatment of Cirrhosis of Liver by Nutritious Diet and Supplements Rich in Vitamin B Complex, J. Clin. Investigation **20**:481 (Sept.) 1941. (*c*) Best, C. H.; Hershey, J. M., and Huntsman, M. E.: The Control of the Deposition of Liver Fat, Am. J. Physiol. **101**:7 (June) 1932. Best, C. H., and Huntsman, M. E.: Effects of Components of Lecithine upon Deposition of Fat in Liver, J. Physiol. **75**:405 (Aug.) 1932. Best, C. H., and Ridout, J. H.: Effects of Cholesterol and Choline on Deposition of Liver Fat, ibid. **78**:415 (July 10) 1933. Best, C. H.; Ferguson, G. C., and Hershey, J. M.: Choline and Liver Fat in Diabetic Dogs, ibid. **79**:94 (July 28) 1933. Best, C. H.; Channon, H. J.,

(Footnote continued on next page)

toxic hepatitis in experimental animals by feeding brewers' yeast. Patek and Post [33b] have observed pronounced clinical improvement in patients with cirrhosis of the liver following the ingestion of large amounts of brewers' yeast. Best and co-workers' [33c] observation that choline inhibits the accumulation of neutral fat and cholesterol esters in the liver and accelerates their disappearance from the liver has provided new therapeutic possibilities in hepatic and pancreatic diseases. Their observations on the similar action of protein [33d] has been supplemented by the observations of Ravdin and his collaborators [33e] on the protective effect of this lipotropic action on the liver. There appears to be some question as to whether the beneficial effect of Dragstedt's lipocaic [33f] is due to its choline and protein content or to some other specific substance.[33g]

Andersen [34] has reviewed and augmented the evidence of an impaired intestinal absorption of vitamin A and the need of large doses of the fat-soluble vitamins in cystic fibrosis of the pancreas. Parsons,[35] Clausen and McCoord [12a] and co-workers [36] and May, Blackfan, McCreary and Allen [37] have provided ample evidence of poor absorption of the fat-soluble vitamins in celiac disease. As long ago as 1929 Haas [38] recorded his belief that some of the symptoms of celiac disease were manifestations of deficiencies of vitamin B. Fullerton and Innes [39] noted the multiple nature of the nutritional deficiencies in idiopathic steatorrhea.

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and Ridout, J. H.: Choline and Dietary Production of Fatty Livers, ibid. **81**:409 (July 31) 1934. Best, C. H.; Maclean, D. L., and Ridout, J. H.: Choline and Liver Fat in Phosphorous Poisoning, ibid. **83**:275 (Feb. 9) 1935. (*d*) Best, C. H., and Ridout, J. H.: The Pancreas and the Deposition of Fat in the Liver, Am. J. Physiol. **122**:67 (April) 1938. (*e*) Goldschmidt, S.; Vars, H. M., and Ravdin, I. S.: Influence of Foodstuffs upon Susceptibility of Liver to Injury by Chloroform, and Probable Mechanism of Their Action, J. Clin. Investigation **18**:277 (May) 1939. Ravdin, I. S.: Protection of Liver from Injury, Surgery **8**:204 (Aug.) 1940. (*f*) Dragstedt, L. R.: Present Status of Lipocaic, J. A. M. A. **114**:29 (Jan. 6) 1940. (*g*) Best, C. H., and Ridout, J. H.: Choline as Dietary Factor, in Luck, J. M., and Smith, J. H. C.: Annual Review of Biochemistry, Stanford University, Calif., Annual Reviews, Inc., 1939, vol. 8, p. 349.

34. Andersen, D. H.: Cystic Fibrosis of Pancreas and Its Relation to Celiac Disease: Clinical and Pathologic Study, Am. J. Dis. Child. **56**:344 (Aug.) 1938.

35. Parsons, L. G.: Celiac Disease: Rachford Memorial Lectures, Am. J. Dis. Child. **43**:1293 (May, pt. 2) 1932.

36. Chesney, J., and McCoord, A. B.: Vitamin A of Serum Following Administration of Haliver Oil in Normal Children and in Chronic Steatorrhea, Proc. Soc. Exper. Biol. & Med. **31**:887 (April) 1934. Breese, B. B., Jr., and McCoord, A. B.: Vitamin A Absorption in Celiac Disease, J. Pediat. **15**:183 (Aug.) 1939.

37. May, C. D., and McCreary, J. F.: Absorption of Vitamin A in Celiac Disease: Interpretation of Vitamin A Absorption Test, J. Pediat. **18**:200 (Feb.) 1941. May, Blackfan, McCreary and Allen.[12c]

38. Haas, S. V.: Beriberi in Late Infancy: The Result of Celiac Disease, Am. J. Dis. Child. **37**:1111 (May) 1929.

39. Fullerton, H. W., and Innes, J. A.: Case of Idiopathic Steatorrhoea, with Multiple Nutritional Deficiencies, Lancet **2**:790 (Oct. 3) 1936.

Albright and Stewart [40] have shown the extensiveness of the hypovitaminosis of all the fat-soluble vitamins and of the disturbance in steroid metabolism incident to steatorrhea. Examination of 1 of the patients in this clinic with early ulcerative colitis revealed multiple deficiencies, as evidenced by abnormally low values for the following determinations: weight; red blood cell count and hemoglobin; serum protein, chloride, sodium, calcium, vitamin A, carotenoids and cholesterol; ascorbic acid in the plasma and in the white blood cells and platelets; free and total gastric hydrochloric acid before and after ingestion of histamine; duodenal enzymes, and twenty-four hour excretion of urinary steroids. Abt, Farmer and Topper [41] have demonstrated the poor absorption of ascorbic acid in the presence of diarrhea.

There is much evidence to suggest that a nutritional disturbance may lead to a deficiency of the vitamin B complex,[42] which in turn introduces alterations in gastrointestinal function that result in a chronic intestinal disturbance. The delayed gastric emptying and reduced motility of the small intestine with segmental dilatation and contraction observed in nontropical sprue, idiopathic steatorrhea, pancreatic fibrosis and celiac disease [43] are likewise found in B complex deficiency.[44] The observa-

40. Albright, F., and Stewart, J. D.: Hypovitaminosis of All Fat-Soluble Vitamins Due to Steatorrhea: Report of Case, New England J. Med. **223**:239 (Aug. 15) 1940.

41. Abt, A. F.; Farmer, C. J., and Topper, Y. J.: Influence of Catharsis and Diarrhea on Gastrointestinal Absorption of Ascorbic Acid in Infants, Proc. Soc. Exper. Biol. & Med. **43**:24 (Jan.) 1940.

42. Bean, W. B., and Spies, T. D.: Vitamin Deficiencies in Diarrheal States, J. A. M. A. **115**:1078 (Sept. 28) 1940.

43. Mackie, T. T.: Nontropical Sprue, M. Clin. North America **17**:165 (July) 1933. Snell, A. M., and Camp, J. D.: Chronic Idiopathic Steatorrhea: Roentgenologic Observations, Arch. Int. Med. **53**:615 (April) 1934. Mackie, T. T., and Pound, R. E.: Changes in Gastro-Intestinal Tract in Deficiency States, with Special Reference to Small Intestine: Roentgenologic and Clinical Study of Forty Cases, J. A. M. A. **104**:613 (Feb. 23) 1935. Mackie, T. T.; Miller, D. K., and Rhoads, C. P.: Sprue: Roentgenologic Changes in Small Intestine, Am. J. Trop. Med. **15**: 571 (Sept.) 1935. Golden, R.: Small Intestine and Diarrhea, Am. J. Roentgenol. **36**:892 (Dec.) 1936. Kantor, J. L.: Roentgen Diagnosis of Idiopathic Steatorrhea and Allied Conditions: Practical Value of "Moulage Sign," ibid. **41**:758 (May) 1939. May and others.[12e]

44. McCarrison, R.: Faulty Food in Relation to Gastro-Intestinal Disorder, J. A. M. A. **78**:1 (Jan. 7) 1922. Gross, L.: Effects of Vitamin Deficient Diets on Rats, with Special Reference to Motor Functions of Intestinal Tract in Vivo and in Vitro, J. Path. & Bact. **27**:27 (Jan.) 1924. Cowgill, G. R.; Deuel, H. J., Jr.; Plummer, N., and Messer, F. C.: Studies on the Physiology of Vitamins: IV. Vitamin B in Relation to Gastric Motility, Am. J. Physiol. **77**:389 (July) 1926. Fletcher, A. A., and Graham, D.: The Large Bowel and Chronic Arthritis, Am. J. M. Sc. **179**:91 (Jan.) 1930. Elsom, K. O.: Experimental Study of Clinical

(Footnote continued on next page)

tion of Melnick, Robinson and Field [45] that gastric achlorhydria favors the destruction of thiamine suggests that the achlorhydria so frequently present in chronic nutritional disturbances may be a factor favoring B deficiency. The observation that niacin decreases and inositol increases [46] the peristaltic action of the stomach and small intestine may indicate that a balance of B factors is essential to proper gastrointestinal function. Such a role for these factors would explain the sporadic improvement that has been observed by many to follow the administration of liver extract or vitamin B concentrates to infants with chronic nutritional disturbances and older patients with celiac disease. The effect of thiamine deficiency on the heart, as demonstrated by Weiss and Wilkins [47] suggested the attention that should be given to the vitamin B nutrition of persons suffering cardiac decompensation or circulatory embarrassment from any cause, particularly if there is a concomitant limitation to the ingestion of food.

The well known interdependence of dextrose, phosphates and certain enzymes in cellular metabolism [3] would suggest that infants who are vomiting and stooling and receiving large daily infusions of only dextrose and sodium chloride solution would appear to be excellent candidates for at least phosphate and vitamin B deficiencies. Haldane and co-workers [48] have called attention to the loss of phosphate incident to an acidosis similar to that which occurs so frequently in patients with these nutritional defects. The need of and the beneficial effect of phosphate on such infants are suggested by Guest and Rapoport's

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Vitamin B Deficiency, J. Clin. Investigation **14**:40 (Jan.) 1935. Elsom, K. O.; Lewy, F. H., and Heublein, G. W.: Clinical Studies of Experimental Human Vitamin B Complex Deficiency, Am. J. M. Sc. **200**:757 (Dec.) 1940. Golden, R.: Abnormalities of Small Intestine in Nutritional Disturbances: Some Observations on Their Physiologic Basis (Carman Lecture), Radiology **36**:262 (March) 1941; Small Intestine in Vitamin B Deficiency, J. A. M. A. **117**:913 (Sept. 13) 1941. Lepore, M. J., and Golden, R.: Syndrome Due to Deficiency of Vitamin B Complex, ibid. **117**:918 (Sept. 13) 1941. Mackie, T. T.: Vitamin Deficiencies and Small Intestine, ibid. **117**:910 (Sept. 13) 1941. Bean and Spies.[42]

45. Melnick, D.; Robinson, W. D., and Field, H., Jr.: Fate of Thiamine in Digestive Secretions, J. Biol. Chem. **138**:49 (March) 1941.

46. Martin, G. J.; Thompson, M. R., and de Carvajal-Forero, J.: Influence of Inositol and Other B Complex Factors upon Motility of Gastro-Intestinal Tract, Am. J. Digest. Dis. **8**:290 (Aug.) 1941.

47. Weiss, S., and Wilkins, R. W.: Nature of Cardiovascular Disturbances in Nutritional Deficiency States (Beriberi), Ann. Int. Med. **11**:104 (July) 1937. Weiss, S.: Occidental Beriberi with Cardiovascular Manifestations: Its Relation to Thiamin Deficiency, J. A. M. A. **115**:832 (Sept. 7) 1940.

48. Haldane, J. B. S.; Wigglesworth, V. B., and Woodrow, C. E.: The Effect of Reaction Changes on Human Inorganic Metabolism, Proc. Roy. Soc., London, s.B **96**:1, 1924.

observations [49] on the concentration of organic acid-soluble phosphorus in the red blood cells and on the effectiveness of phosphate in the parenteral therapy of dehydrated and acidotic patients. But as yet proof of the existence of deficiencies of vitamin B under such circumstances is meager.[50] New methods for detecting such deficiencies are now being reported, which may permit their earlier recognition. Bueding and Wortis [51] recently have introduced a pyruvic acid tolerance curve for appraising thiamine deficiency. Holt and Najjar [52] have just reported a simple urinary excretion method for detecting thiamine, riboflavin and niacin deficiencies. The observation of Rhoads and co-workers [53] on the high thiamine content of white blood cells may lead to their thiamine content being shown to be an index of thiamine nutrition.

Stewart and Rourke [54] have shown that rapid infusions of dextrose alone may cause a failure of renal conservation of sodium, a pronounced reduction in plasma sodium concentration and serious symptoms progressing from nausea to vomiting, disorientation, convulsions and coma. The ready availability of properly balanced solutions of chloride and sodium [55] should not only prevent the occurrence of such a syndrome in clinical medicine but also result in more appropriate parenteral therapy for dehydration accompanied by acidosis [56] than is provided by 0.85 per

49. Guest, G. M., and Rapoport, S.: Role of Acid-Soluble Phosphorus Compounds in Red Blood Cells in Experimental Rickets, Renal Insufficiency, Pyloric Obstruction, Gastroenteritis, Ammonium Chloride Acidosis and Diabetic Acidosis, Am. J. Dis. Child. **58**:1072 (Nov.) 1939; Acid-Soluble Phosphorus of Red Blood Cells in Diabetic Acidosis, ibid. **60**:450 (Aug.) 1940; Clinical Studies of Organic Acid-Soluble Phosphorus of Red Blood Cells in Different Acidotic States, J. Lab. & Clin. Med. **26**:190 (Oct.) 1940.

50. Najjar, V. H., and Holt, L. E., Jr.: Studies in Thiamin Excretion, Bull. John Hopkins Hosp. **67**:107 (Aug.) 1940. Spies, T. D.; Bean, W. B.; Vilter, R. W., and Huff, N. E.: Endemic Riboflavin Deficiency in Infants and Children, Am. J. M. Sc. **200**:697 (Nov.) 1940.

51. Bueding, E., and Wortis, H.: J. Clin. Investigation, to be published.

52. Holt, L. E., Jr., and Najjar, V. H.: Paper read at the annual meeting of the American Pediatric Society, May 1942.

53. Gorham, A. T.; Abels, J. C.; Robins, A. L., and Rhoads, C. P.: The Measurement and Metabolism of Thiamin and of a Pyrimidine Stimulating Yeast Fermentation Found in the Blood Cells and Urine of Normal Individuals, J. Clin. Investigation **21**:161 (March) 1942.

54. Stewart, J. D., and Rourke, G. M.: The Effects of Large Intravenous Infusions on Body Fluid, J. Clin. Investigation **21**:197 (March) 1942.

55. Hartmann, A. F., and Senn, M. J. E.: Studies in Metabolism of Sodium r-Lactate: Response of Normal Human Subjects to Intravenous Injection of Sodium r-Lactate, J. Clin. Investigation **11**:327 (March) 1932; Studies in Metabolism of Sodium r-Lactate; Response of Human Subjects with Acidosis to Intravenous Injection of Sodium r-Lactate, ibid. **11**:337 (March) 1932.

56. Hartmann, A. F.; Perley, A. M.; Basman, J.; Nelson, M. V., and Asher, C.: Further Observations on Metabolism and Clinical Uses of Sodium Lactate, J. Pediat. **13**:692 (Nov.) 1938. Butler, A. M.: Electrolyte and Water Balance, New England J. Med. **220**:827 (May 18) 1939.

cent sodium chloride solution. Moreover, the recent report of Astwood and Flynn [57] indicates that more than a certain amount of intravenous dextrose, even when administered with sodium chloride solution by slow continuous drip, may cause profound and deleterious effects. Thus, the increasing availability of serum, of preparations of hydrolyzed casein for intravenous use [58] and of crystalline vitamins is augmenting the nutritional potentialities of the heretofore obviously inadequate parenteral therapy.

Even this brief review indicates the immense mass of clinically applicable knowledge which has derived from recent advances in nutrition. Yet in many ways this new knowledge has simplified the clinical management of nutritional disturbances. It is clarifying their causation and providing potentialities in therapeutic nutrition that may play no small part in attaining the ultimate goal of better health.

Massachusetts General Hospital.

57. Astwood, E. B., and Flynn, J. M.: Paper read at the annual meeting of the American Society for Clinical Investigation, May 1942.

58. Shohl, A. T.; Butler, A. M.; Blackfan, K. D., and MacLachlan, E.: Nitrogen Metabolism During Oral Parenteral Administration of Amino Acids of Hydrolyzed Casein, J. Pediat. **15**:469 (Oct.) 1939. Farr, L. E.; Emerson, K., Jr., and Futcher, P. H.: Comparative Nutritive Efficiency of Intravenous Amino Acids and Dietary Protein in Children with Nephrotic Syndrome, ibid. **17**:595 (Nov.) 1940.

News and Comment

SPECIAL NOTICE

An Appeal.—Several thousand children of Polish, German, Russian, Czechoslovakian, Dutch and other nationalities, now in Southern France, are in grave danger of deportation to eastern Europe unless they are brought to America quickly. For the most part their parents are already gone or likely to be deported immediately, and the children themselves are in a condition of forlorn hope.

The United States Committee for the Care of European Children, Inc., has undertaken to bring as many children as are eligible under the existing limitations and within the regulations of immigration procedure to the United States, where they will be placed in private homes. Many agencies are assisting in bringing the children from unoccupied France across Spain to Lisbon, Portugal, and from Lisbon to the United States on neutral boats, which boats will sail with navicerts provided by the respective governments.

Plans have been completed for a first escort party of seven doctors, six nurses, four nurses' aides and twenty persons trained in child care who are used to handling children in large groups to go from this country to Lisbon, whence they will return with the convoy of children. The American escorts will be supplemented by additional escorts, carefully picked from refugees abroad. The returning steamer will be crowded, and there is considerable danger from epidemics; but, even so, the temporary conditions of such a passage, bad as they may be, are far better than the only remaining alternative which faces the children—that of deportation into eastern Europe. Thus, without question, as many children as it is physically possible to bring to a free country should be given such an opportunity.

A brief announcement at one meeting of the section on pediatrics of the New York Academy of Medicine recently produced more than enough volunteers among the physicians to cover the first trip. If this trip is successful, it is expected that there will be other trips in the course of the winter and spring, and physicians, nurses and qualified escorts will be needed for these anticipated voyages. All volunteers must be citizens of the United States, have a special knowledge of either French or German, be willing to work almost ceaselessly on the eleven or twelve days of the return trip and be willing to do anything that needs be done. Of the physicians there are needed for each trip: one surgeon, one child psychiatrist and pediatricians. All expenses of each volunteer will be paid. Physicians will receive no additional honorarium.

Physicians interested in making such trips should communicate directly with Dr. Philip M. Stimson, 25 Claremont Avenue, New York. All others should communicate with Mr. Robert Lang, Director, United States Committee for the Care of European Children, 215 Fourth Avenue, New York.

PERSONAL NEWS

Dr. Lawrence T. Royster Retired.—Dr. Lawrence T. Royster has been retired as head of the department of pediatrics of the University of Virginia Department of Medicine, University, Va. Dr. Royster was the first professor of pediatrics at this school, taking the chair in 1923. This was a labor of love for Dr. Royster, since he left a large practice in Norfolk to assume this duty, and that he has been successful in his work is shown by the many men who

have served under him and have done excellent work in pediatrics as well as by the pediatric work in his region, which has been so favorably influenced by his efforts.

GENERAL NEWS

National Foundation for Infantile Paralysis.—The third annual medical meeting of the National Foundation for Infantile Paralysis will be held in New York on Dec. 3 and 4, 1942.

DEATHS

Dr. David J. Levy, one of the prominent pediatricians of Detroit and one of the earlier pediatricians in the country, died suddenly at his home on October 14.

CORRECTION

In the article by Dr. George M. Guest entitled "Organic Phosphates of the Blood and Mineral Metabolism in Diabetic Acidosis," in the September issue (AM. J. DIS. CHILD. **64**:401, 1942), three errors occurred: In the diagram at the bottom of page 402, the left of the lower pair of arrows should point up instead of down. In the last line of the legend for chart 4, on page 407, the chart numbers should be 2 and 3. The third line from the bottom of page 408 should begin "the carbon dioxide content *and* the p_H of the blood."

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

ACTINOMYCES ANTIBIOTICUS, A NEW SOIL ORGANISM ANTAGONISTIC TO PATHOGENIC AND NON-PATHOGENIC BACTERIA. SELMAN A. WAKSMAN and H. BOYD WOODRUFF, J. Bact. **42**:231 (Aug.) 1941.

The authors found a species of actinomyces possessing strong bacteriostatic and bactericidal properties could be isolated from the soil. This organism was found to belong to the chromogenic types of actinomycetes, producing brown to black pigments on peptone and protein mediums. With use of solvents, such as ethyl ether, purified petroleum benzene (petroleum ether), ethyl alcohol and chloroform, cultures of this organism yielded an active substance which could be separated into two crystalline fractions, called actinomycin A and actinomycin B. The first fraction was found to be highly bacteriostatic, whereas the second had little bacteriostatic action but was often strongly bactericidal. Actinomycin A was found to possess bacteriostatic properties against all bacteria tested. Although gram-positive bacteria are much more sensitive to this substance than are gram-negative organisms, there was found a great variation in the degree of sensitivity among the various bacteria within each of these two groups.

STOESSER, Minneapolis.

FURTHER OBSERVATIONS ON PENICILLIN. E. P. ABRAHAM and others, Lancet **2**:177 (Aug. 16) 1941.

Penicillin is a product of mold growth. It combines to a striking degree two most desirable qualities of a chemotherapeutic agent: low toxicity to tissue cells and powerful bacteriostatic action.

A description is given of the cultural and other conditions required for the effective production of penicillin by Penicillium notatum.

Observations on the absorption and excretion of the drug were made on the rabbit, the cat and man.

Growth in vitro of many pathogenic bacteria is prevented by purified penicillin at a dilution of 1 to 1,000,000 or more.

The antibacterial activities of penicillin and of sulfonamide compounds are compared, and reasons are adduced why penicillin can be expected to operate when sulfanilamide or one of its derivatives is inactive.

Although it has been used therapeutically in some subjects with apparently good results, the number of such trials is still too small to permit drawing of conclusions.

LANGMANN, New York.

THE HISTORY OF SALMONELLA INFECTION IN HAVANA. A. CURBELO and JUAN A. MARTINEZ CRUZ, Arch. de med. inf. **10**:170 (July-Sept.) 1941.

The authors present a detailed historical report of the 1936 epidemic in Habana, Cuba. The organism, heretofore unknown, which caused the disease was named "Salmonella havana."

SANFORD, Chicago.

Metabolism; Infant Feeding; Milk and Other Foods

DESICCATED BEEF AS A FOOD FOR PREMATURE AND FULL TERM INFANTS. HEYWORTH N. SANFORD and LEO K. CAMPBELL, Arch. Pediat. **58**:504 (Aug.) 1941.

The meat used was ground fat-free round steak, desiccated at 56 F. in vacuum and pulverized. The iron content of various samples varied between 1 and 0.67 per cent.

The period of study covered twelve months and included 102 infants. No infants are included in the report who were not followed for at least six months. All were artificially fed on the same well balanced diet, varied according to their respective ages. Forty-eight full term infants received the standard diet plus daily amounts of 1 teaspoonful of desiccated beef added to the formula. This was increased to 4 teaspoonfuls as soon as possible.

There were 13 premature infants in this study. All weighed between 3½ pounds (1,534 Gm.) and 5 pounds (2,268 Gm.) at birth, and all weighed 5½ pounds (2,495 Gm.) to 6 pounds (2,722 Gm.) and had a hemoglobin content of 70 per cent when they left the hospital at between 1 and 2 months of age. After their discharge from the hospital, they were placed on the standard diet. Six of the premature group were given 30 drops of a 50 per cent solution of iron and ammonium citrates (U. S. P.) daily. Seven received desiccated beef in place of iron and ammonium citrates. The premature group tolerated desiccated beef about as well as the full term group. Three did, however, have loose stools.

The authors' conclusions were that desiccated beef is a suitable food for full term infants over 6 weeks of age and also for most premature infants. As an additional food it had no influence on weight or on hemoglobin and red cell content of the blood of full term infants during the first year of life. Desiccated beef will give premature infants a blood hemoglobin content and red cell count comparable to the values found when premature infants were given iron and ammonium citrates.

ORR, Buffalo.

HISTOLOGICAL STUDIES OF THE TISSUES OF RATS FED A DIET EXTREMELY LOW IN ZINC. RICHARD H. FOLLIS JR., HARRY G. DAY and E. V. MCCOLLUM, J. Nutrition **22**:223 (Sept.) 1941.

Rats fed a diet deficient in zinc showed specific pathologic changes in the esophagus and to a lesser extent in the buccal cavity and the skin. A few of the animals also showed vascularization and leukocytic infiltration of the cornea similar to that described in riboflavin deficiency. Follis, Day and McCollum present excellent photomicrographs, showing the extreme parakeratosis of the esophagus, with a thick layer of partially keratinized cells. The skin also showed hyperkeratinization.

FREDEEN, Kansas City, Mo.

THE NUTRITIONAL IMPORTANCE OF CHOLINE. WENDELL H. GRIFFITH, J. Nutrition **22**:239 (Sept.) 1941.

Griffith presents an extensive review of the importance of choline in nutrition. He includes a complete bibliography.

FREDEEN, Kansas City, Mo.

FEEDING THE CHILDREN. Brit. M. J. **2**:454 (Sept. 27) 1941.

This is a short statement concerning the plan to supply dried milk powder to the British public.

ROYSTER, University, Va.

BUTTER MILK AS FOOD FOR INFANTS. O. MEULEMANS and J. H. DE HAAS, Indian J. Pediat. **8**:158 (July) 1941.

For use in infant welfare stations and similar institutions, a method of preparing buttermilk feedings with added cod liver oil and ascorbic acid is described. It consists essentially in using a mixture of spontaneously soured skimmed milk with whole milk and is said to be the cheapest method of preparing a satisfactory diet when the supply of sweet milk is limited.

TENNEY, Madison, Wis.

Vitamins; Avitaminoses

THE RELATION BETWEEN PLASMA AND DIETARY ASCORBIC ACID. A. HUGHES BRYAN, DOROTHEA F. TURNER, RUTH L. HUENEMANN and GERTRUDE LOTWIN, Am. J. M. Sc. **202**:77 (July) 1941.

The authors showed that in healthy human subjects 12 to 35 years of age who are in equilibrium with their diet the level of the fasting plasma ascorbic acid is a function of the average daily intake of the vitamin, the latter perhaps best expressed as intake per kilogram of body weight.

Saturation, with a plasma concentration of approximately 1.0 mg. per hundred cubic centimeters, occurs with intakes ranging from 1.7 to 1.9 mg. of ascorbic acid per kilogram. With lower intakes, the plasma level varies directly with the intake; higher intakes cause little further increase in the plasma level.

From the data reported one can predict the daily intake of ascorbic acid necessary to stabilize a normal subject at a given level of plasma.

Determination of the fasting level of plasma ascorbic acid affords a useful, objective method of characterizing the diet of the normal person in regard to his previous vitamin C intake.

HENSKE, Omaha.

THE INTRACRANIAL AND PERIPHERAL VASCULAR EFFECTS OF NICOTINIC ACID. JULIUS LOMAN, MAX RINKEL and ABRAHAM MYERSON, Am. J. M. Sc. **202**: 211 (Aug.) 1941.

The authors report that nicotinic acid (niacin) was administered by intravenous, intrabrachial and intracarotid routes to a group of subjects for the purpose of comparing the cerebral and peripheral (arm) vascular effects. The following observations were made:

1. The cerebrospinal fluid pressure is insignificantly altered.

2. The caliber of the retinal vessels is unchanged.

3. The cerebral blood flow, using changes in arteriovenous differences in oxygen content as an index, is only slightly increased, while the blood flow in the arm is usually moderately to greatly increased. This difference in response in the two loci is particularly obvious when the drug is injected into the carotid and brachial arteries.

Nicotinic acid (niacin) shortens the Raynaud-like response produced by epinephrine when both drugs are injected into the brachial artery. This peripheral action of the drug suggests a possible usefulness in Raynaud's disease and other peripheral vascular diseases.

HENSKE, Omaha.

THE ASCORBIC ACID CONTENT OF COW'S MILK DURING PREGNANCY. ARTHUR D. HOLMES, FRANCIS TRIPP, E. A. WOELFFER and G. HOWARD SATTERFIELD, J. Nutrition **22**:267 (Sept.) 1941.

Holmes and his colleagues present data which indicate that the vitamin C content of milk from Guernsey and Holstein cows decreases somewhat with the advance of pregnancy, but that there is considerable variation among individual cows.

FREDEEN, Kansas City, Mo.

THE EFFECTS OF VARIOUS VITAMIN SUPPLEMENTS AND OF WHOLE YEAST ON THE DIGESTION AND ABSORPTION OF THE CARBOHYDRATE OF A COMPLETE DIET. R. A. RUSSELL and E. S. NASSETT, J. Nutrition **22**:287 (Sept.) 1941.

Russell and Nassett present evidence showing that digestion and absorption of carbohydrate were hastened by adding the whole vitamin B complex in the form of yeast to an otherwise adequate diet. When the individual components of the B complex were added in excess, there was no effect.

FREDEEN, Kansas City, Mo.

FURTHER OBSERVATIONS ON RIBOFLAVIN AS A FOOD FACTOR IN ECONOMY OF FOOD UTILIZATION. BARNETT SURE, J. Nutrition **22**:295 (Sept.) 1941.

Sure suggests that since riboflavin is a component of the vitamin B complex, which is concerned with the oxidative enzymic processes essential for normal metabolism, a deficiency of this vitamin produces a waste of products of metabolism which results in final collapse of the animal organism. In riboflavin deficiency, unlike thiamine deficiency, there is no complicating anorexia in the terminal stages of the disease.

FREDEEN, Kansas City, Mo.

THE PRODUCTION OF HIGH VITAMIN A MILK BY DIET. HARRY J. DEUEL JR., NELLIE HALLIDAY, LOIS F. HALLMAN, CORNELIA JOHNSTON and ALBERT J. MILLER, J. Nutrition **22**:303 (Sept.) 1941.

Deuel and his colleagues increased the vitamin A content of the butterfat from cows fed a diet high in fresh alfalfa by daily complementing the diet with 700,000 international units of shark liver oil. Lower amounts were ineffective. The carotene content decreased, even when doses of the shark liver oil were too small to cause an increase in the level of vitamin A in the milk.

FREDEEN, Kansas City, Mo.

THE PRESENT STATUS OF ULTRA-VIOLET IRRADIATION. FRANK H. KRUSEN, Brit. J. Phys. Med. **4**:97 (July) 1941.

In the second of a series of two articles the author concludes: Ultraviolet irradiation produces photochemical effects, with activation of substances in the skin and possibly in the blood; biologic effects such as stimulation of metabolism, cellular activity, growth and circulation are also produced; ultraviolet radiation in wavelengths shorter than 315 millimicrons will prevent and cure rickets; these rays, in wavelengths shorter than 315 millimicrons, will impart an antirachitic potency to fats, milk, ergosterol, 7-dehydrocholesterol, oils and vegetables. Such radiation causes delayed or latent erythema of the skin of human beings, improves the tone, color and elasticity of the skin and presumably increases the cutaneous secretory and protective powers. Also irradiation with ultraviolet rays will increase the active oxygen content of the lipids of the skin, thus increasing their bactericidal action.

On general exposure to ultraviolet radiation there will be produced an increase in the number of erythrocytes, leukocytes, blood platelets and hemoglobin of the circulating blood and a decrease in the hydrogen ion concentration, in the coagulation time and eventually in the blood volume. A transient lowering of blood pressure is produced by exposure to ultraviolet rays.

From wavelengths longer than 290 millimicrons there are presumably stimulative effects on the human body. Wavelengths shorter than 290 millimicrons may produce lethal effects on cells of the human body.

General exposures to ultraviolet rays improve muscular tone, increase the metabolism of proteins and minerals and increase the ability of the organism to utilize more effectively materials which are present but not available.

Finally, ultraviolet irradiation will impart an antirachitic potency to the milk of cows or of pregnant or nursing mothers.

HARTMAN, Cleveland.

DARK ADAPTATION TESTS IN CASES OF CLINICAL NIGHT BLINDNESS. K. RAJAGOPAL, Indian J. M. Research **29**:351 (April) 1941.

The author used a modified Birch-Hirschfeld type of adaptometer. He tested 10 clinical patients known to be affected with night blindness and 20 normal controls; none of the subjects was below 11 years of age. He ran the test for forty-five minutes. He states that it cannot be applied to a young or mentally dull person. He found a slower rate of adaptation and a higher final visual threshold after exposure to bright light in those suffering from night blindness than in

the normal subjects. He administered 216,000 international units of vitamin A and found great improvement within six hours and a normal curve within forty-eight hours.

SNELLING, Toronto, Canada.

XEROPHTHALMIA IN CHILDREN IN BATAVIA. J. H. DE HAAS, J. H. POSTHUMA and O. MEULEMANS, Indian J. Pediat. **8**:139 (July) 1941.

Of all children admitted to Central Civil Hospital in Batavia, Netherlands East Indies, nearly 5 per cent had xerophthalmia and 40 to 45 per cent became blind in one or both eyes. The mortality rate was no higher than in children without xerophthalmia. One quarter of the infants under 2 years were breast fed. Sweetened skimmed milk was responsible in 0.66 per cent of the cases. Advanced malnutrition was present in 75 per cent. The vitamin A content of the blood was lower than in normal children, but both groups had lower levels of the vitamin than normal adults. Further study of this phase of the problem is necessary. Treatment in the first few days consisted of parenteral administration of vitamin A followed by cod liver oil. Prophylaxis is more important than treatment and requires improved nutrition of the preschool child.

TENNEY, Madison, Wis.

ON THE PLASMA PHOSPHATASE TITER IN RICKETS WITH PARTICULAR REFERENCE TO THE SHOCK TREATMENT. EINAR JOSEFSSON, Ann. pædiat. **157**:169 (Sept.) 1941.

Determination of the values for phosphatase constitutes a valuable complement to the other investigations in cases of rickets, both as a criterion of the presence of the disease and to some extent as a gauge of its degree. In both these respects the phosphatase values are to be regarded as a more delicate index than the ordinary blood phosphorus values. Josefsson's opinion on this matter thus corresponds with that of earlier investigators.

Phosphatase determinations are also valuable and of indubitably greater interest than blood phosphorus determinations when one is judging the shock treatment clinically. If the phosphatase level is normal before the treatment, little can be expected of later determinations. If it is moderately increased (up to about 500 units), on the other hand, a reduction immediately after the treatment probably indicates that the disease is mild or moderately severe. But if the value remains high for some time, instead of dropping soon after the treatment, there is reason to assume that the disease is more severe. A really high value, such as 600 units or more, indicates genuine rickets.

AUTHOR'S SUMMARY.

Newborn

STERNAL MARROW CHANGES DURING THE FIRST WEEK OF LIFE: CORRELATION WITH PERIPHERAL BLOOD FINDINGS. LAWRENCE M. SHAPIRO and FRANK A. BASSEN, Am. J. M. Sc. **202**:341 (Sept.) 1941.

Studies of peripheral blood and sternal punctures were made on 35 normal full term infants in the first twenty-four hours of life and again one week later.

On the peripheral blood the observations of these authors agreed with those of many other investigators. They noted initial high levels of red cells, hemoglobin, white cells and reticulocytes. There were a moderate decrease in red cells and hemoglobin, a sharp fall in white cells and reticulocytes and a change in the differential count from myeloid to lymphocytic predominance at the end of the week.

The most striking change observed in the bone marrow was a pronounced drop in the erythroid elements at the end of the first week of life. This condition, reflected in the peripheral blood by the decrease in the number of reticulocytes, is evidence of curtailed production of new red cells. Consequently the authors offer the idea that the decrease in red cells and hemoglobin which takes place after

birth is primarily the result of physiologic disintegration of the superabundant red cells carried over from fetal life in the presence of diminished erythropoiesis.

HENSKE, Omaha.

EFFECT OF TOPICAL APPLICATION OF 2-METHYL-1,4-NAPHTHOQUINONE (SYNTHETIC VITAMIN K ANALOGUE) ON THE PROTHROMBIN LEVEL OF NEWBORN INFANTS, WITH REFERENCE TO A SIMPLIFIED MICRO-PROTHROMBIN TEST. H. K. RUSSELL and ROBERT C. PAGE, Am. J. M. Sc. **202**:355 (Sept.) 1941.

Russell and Page state that this simplified test, which requires no special apparatus or unstable reagents, can be performed by the practitioner at the bedside.

Data have been presented in this study showing that the percutaneous application of menadione (2-methyl-1,4-naphthoquinone, synthetic vitamin K analogue) in an ointment base will prevent hypoprothrombinemia of the newborn. As this method is simple and effective, it is suggested that it be used routinely as a prophylactic measure in preventing hypoprothrombinemia of the newborn. As a routine procedure, 10 mg. of menadione in a special ointment can be rubbed thoroughly on the skin of the back during the first or second day of life. As a single application was effective in the authors' series, they do not believe that the application need be repeated.

HENSKE, Omaha.

THE EFFECTIVENESS OF PRENATAL ADMINISTRATION OF 2-METHYL-1,4-NAPHTHOQUINONE IN MAINTAINING NORMAL PROTHROMBIN LEVELS IN INFANTS. ELEANOR H. VALENTINE, JOHN G. REINHOLD and ERICH SCHNEIDER, Am. J. M. Sc. **202**:359 (Sept.) 1941.

About three fourths of the infants of untreated mothers exhibited a significant drop to an abnormally low average prothrombin level within forty-eight to ninety-six hours after birth, with a rise to a normal level by the end of the first week.

Infants whose mothers had received menadione (2-methyl-1,4 naphthoquinone) from five to twenty-eight days prior to delivery were protected against the fall in prothrombin in all but 2 of 23 cases.

Occasional subnormal prothrombin levels were observed in a group of 50 pregnant women examined shortly before term.

HENSKE, Omaha.

FOUR PHASES OF BIRTH. JOSEPH BARCROFT, Lancet **2**:91 (July 26) 1941.

The author takes up the more accurate description of birth under four headings: (1) change in atmosphere; (2) transfer of blood from the placenta to the fetus; (3) alterations in the thoracic circulation, and (4) the first breath.

This study is based chiefly on experiments with lambs.

During the latter half of the period of gestation in the sheep the quantity of fetal blood in the placenta remains relatively constant, while with the growth of the placenta the blood volume of the fetus increases as much as six to eight times. The growth requirements of the fetus are met in the placenta by an increased rapidity of blood flow and by increased quantities of hemoglobin in the blood.

A considerable volume of the fetal blood circulating in the placenta is transferred to the fetus at birth. The excess corpuscles are broken down, and the iron is stored.

Evidence is given of the functional closing of the foramen ovale and the ductus arteriosus within a few minutes of birth. This was obtained by the taking of roentgenograms after intravenous injection of colloidal thorium dioxide (thorotrast).

Evidence is also given showing that the essential neuromuscular mechanism for drawing the first breath is laid down between the thirty-fourth and the fiftieth day of gestation and that asphyxia, far from stimulating the early spasmodic rhythms of the respiratory type, actually depresses them. At this stage, exposure or asphyxia fails to excite activity in the embryo.

By the sixtieth day of gestation higher levels of the brain have developed sufficiently to inhibit the lower centers, so that the 60 day fetus appears much more inert than the active 50 day fetus. Asphyxia depresses the higher centers and liberates the lower centers, thus converting the inert 60 day fetus functionally to the active 50 day fetus. Exposure has the same effect.

At birth the lamb experiences both partial asphyxia, because of suspension of the placental circulation, and exposure. It responds with the respiratory movement which it developed some hundred days before. Sensory impulses from the skin heighten the tendency toward respiration. LANGMANN, New York.

ICTERUS GRAVIS NEONATORUM CURED BY SPLENECTOMY. CHRISTOPHER HARDWICK and OSWALD LLOYD, Lancet **2**:339 (Sept. 20) 1941.

A boy with typical features of icterus gravis neonatorum had a splenectomy done at the age of 75 hours, with excellent results. The infant was severely ill; jaundice appeared early and became deep; the liver and spleen were enlarged. In spite of two blood transfusions the number of red cells and the percentage of hemoglobin fell rapidly. LANGMANN, New York.

HEMORRHAGE, ANEMIA AND JAUNDICE IN THE NEW-BORN. F. ARDEN, M. J. Australia **2**:343 (Sept. 27) 1941.

Arden regards the three physiologic states of the newborn (a tendency to hemorrhage, anemia and jaundice) and the corresponding pathologic states as related and as blending imperceptibly into one another. In a large maternity hospital babies can be found who represent every transitional stage from those whose latent tendencies can be discovered only by biochemical means to those with a fulminating illness which kills them in a few hours. Hemorrhagic disease is not uncommon (1 case to every 390 births in the author's experience); it can be prevented by antepartum administration of vitamin K to the mother and can be cured by vitamin K and intravenous and intramuscular injections of blood. Anemia of prematurity is unaffected by iron, but blood transfusion sometimes saves a life. Congenital hemolytic anemia may be the result of an exaggeration of the normal hemolytic process of the newborn, but it probably is due to the effect of a primary autogenous hemolysin. The strikingly beneficial result of blood transfusion possibly comes from the supply of an antihemolysin. Physiologic jaundice and icterus gravis are related and probably represent different degrees of hepatic damage from the same toxic agent. Destruction of the excessive red cells occurs in all newborn babies, but it cannot account for physiologic jaundice, because only 1 child in 3 becomes actually jaundiced. Hemolysis of red cells and necrosis of liver cells are two entirely separate processes, although they often occur simultaneously in the same infant. The hemorrhagic tendency in icterus gravis can be attributed to hepatic damage. GONCE, Madison, Wis.

Acute Contagious Diseases

ACTIVE IMMUNIZATION AGAINST TETANUS AND DIPHTHERIA IN INFANTS AND CHILDREN. J. A. BIGLER and MARIE WERNER, J. A. M. A. **116**:2355 (May 24) 1941.

As a result of studies with tetanus toxoid alone and combined with diphtheria toxoid the authors prove its feasibility. Two injections of the alum-precipitated toxoid provide a basic immunity, which can be raised by a stimulative dose above the protective level of 1,500 units (American) of antitoxin. Failures were infrequent, as with diphtheria immunization. HEERSMA, Kalamazoo, Mich.

THE PATHOLOGY OF MUMPS ENCEPHALITIS WITH REPORT OF A FATAL CASE. W. L. DONOHUE, J. Pediat. **19**:42 (July) 1941.

Encephalitis developed in a 5 year old girl seven days after the onset of bilateral parotitis. Death occurred four days later. An autopsy was performed two hours after death. The characteristic lesion throughout the parenchyma was essentially a perivascular demyelination with attendant reaction on the part of the glial and mesodermal tissues. These changes were found in the white matter of the cerebral hemispheres, the cortex and the basal nuclei being spared, in the white matter of the cerebellum, including the dentate nucleus, and in the midbrain, the pons, the medulla and the cord. The lesions in the cord were severe in the cervical region but decreased in severity at lower levels. In all portions of the brain and cord involved there was a perivascular infiltration with many microglia cells and some swelling and proliferation of the astrocytes. Most of the cells were immediately outside the Virchow-Robin space in the adjacent parenchyma. The main infiltrating cell had a darkly staining irregular-shaped nucleus. The infiltration extended out from the blood vessels into the parenchyma, decreasing in intensity and gradually merging with the surrounding normal tissue. This zone of infiltration corresponded to the zone of demyelination in which the myelin sheaths adjacent to the blood vessels showed all stages of degeneration. The histologic picture found in this case falls definitely into the well recognized group of the so-called postinfection encephalitides or acute perivascular myelinoclases which may follow such diseases as smallpox, chickenpox, measles and vaccination.

RAUH, Cincinnati.

PARAPERTUSSIS: CLINICAL AND SEROLOGIC OBSERVATIONS. J. J. MILLER JR., T. M. SAITO and R. J. SILVERBERG, J. Pediat. **19**:229 (Aug.) 1941.

Ten cases of infections of the respiratory tract in children due to Bacillus parapertussis are described. Only 2 presented the classic picture of whooping cough, and in 2 more the clinical diagnosis was mild whooping cough. The remainder presented the symptoms of tracheitis or infection of the upper respiratory tract. Two of the children had had whooping cough previously, and 3 had been given Haemophilus pertussis vaccine. In 2 other children typical pertussis occurred seven months and one year, respectively, after the attack of parapertussis. Thus apparently cross protection does not occur. In 3 instances in which time exposure was known, the incubation periods were six, twelve and fifteen days. The appearance of specific agglutinins was demonstrated in all of the 10 cases. The agglutinins persisted for as long as forty months. Nonspecific H. pertussis agglutinins did not appear and were found only in the serums of those children who had also had pertussis or H. pertussis vaccine. Bacillus parapertussis agglutinins were also found in 40 per cent of the children with no history of parapertussis, pertussis or inoculation with H. pertussis vaccine. This suggested that the incidence of unapparent B. parapertussis infections in this community is relatively high. It was observed that attacks of pertussis and injections of H. pertussis phase I vaccine may on rare occasions give rise to the production of nonspecific parapertussis antibody in low titer. The development of specific mouse-protective antibody in the serum of 3 patients with parapertussis was observed.

RAUH, Cincinnati [AUTHORS' SUMMARY].

VARICELLA AND HERPES ZOSTER WITH A REPORT OF THREE ILLUSTRATIVE CASES. R. M. CAMPBELL, Brit. J. Child. Dis. **38**:91 (July-Sept.) 1941.

Campbell reports 3 cases (1 patient a boy of 14 months, 1 a woman of 49 years and 1 a man of 28 years) in which the vesicular lesions characteristic of varicella and of herpes zoster appeared concurrently. In all 3 cases an attack of unilateral herpes zoster affecting two contiguous segmental areas of cutaneous innervation was followed in the same patient by the development of a varicelliform rash at

intervals between five and seven days. The latter eruption was generalized. The commonest sequence is that originally described by von Bokay (1892), in which varicella occurs among contacts of a patient with zoster within the usual incubation period of the former disease. Conversely, instances of herpes zoster following exposure to chickenpox have been recorded.

The relation between zoster and varicella is not fortuitous, but the theory of complete identity is inadequate to explain the facts. The constant finding of elementary bodies in the cutaneous lesions of both diseases and the results of complement-fixation and agglutination reactions give strong support to the view that the virus in both diseases is closely allied, but in the present state of knowledge it is not permissible to claim that they are identical.

LANGMANN, New York.

THYROID HORMONE ESTIMATIONS IN THE "SECOND DISEASE" OF SCARLET FEVER. STEPHAN ZIMÁNYI, Ann. pædiat. **157**:181 (Sept.) 1941.

Although the thyroxin content of the serum showed no characteristic alteration during the period of incubation of scarlatina or in the prodromic and exanthematous stages of the disease, the author was able to observe, dependent on this, whether it was uncomplicated scarlatina or scarlatina followed by a relapse. In uncomplicated scarlatina there was a constant increase of the thyroxin content of the serum after the first period of fever. During a relapse there was a striking decrease of the thyroxin content of the serum and an increase only after a decline or complete expiration of the symptoms.

A successful recovery from the disease goes hand in hand with the increase of the thyroxin content, which agrees with previous experience that a high thyroxin content results in good conditions of immunity. The intensity of formation of thyroid hormone is in close relation to the immunobiologic processes taking place in the organism.

It would be interesting to examine the thyroxin content of the serum in such cases in which the recovery from the disease does not produce a lasting negativity of reaction to the Dick test and in which the immunity reaction follows an incomplete course.

AUTHOR'S SUMMARY.

TWO ATTACKS OF MEASLES. J. GELDRICH, Kinderärztl. Praxis **12**:142 (May) 1941.

For 2 different patients a diagnosis of measles had to be made twice. The second patient was observed in both attacks. He twice presented a fully developed symptom complex, both times with Koplik spots. The source of infection in each attack was known. The author concludes that children can have measles more than once, even though it is a rare occurrence.

HEYMANN, Cleveland.

BACTERIOLOGIC FINDINGS IN COMPLICATIONS OF MEASLES. HERMAN ECK, München. med. Wchnschr. **88**:397 (April 4) 1941.

Eck reports some observations made at the Zwickau hospital during the epidemics of measles of the two preceding years. The patients came almost entirely from nearby camps which housed people who were being transported from neighboring countries back to Germany. During the first year they consisted mostly of peasants who had lived in Poland. There was a variety of complications, of which the most serious was pneumonia. This disease occurred in 28 per cent of the patients and had a fatality rate of 68 per cent. (As the author states, these figures have a special significance because all patients with measles were transferred from the camps to the hospital. In most epidemics only the sickest children are hospitalized; hence the mortality rate of hospital patients is higher than the total fatality rate.) Postmortem cultures were taken from the trachea,

bronchi and lungs. A combinaion of streptococci and staphylococci was found in cultures from 15 patients, and in the culture of another, pneumococci and staphylococci. This agrees with the results of studies made by MacCallum and Henning, who stressed the importance of streptococci in complications of measles.

The following year a similar epidemic occurred in the camps, but this time the people were inhabitants of Bessarabia returning to Germany. From 28 patients with otitis media the purulent discharges were cultured, and in twenty-seven of these cultures Staphylococcus pyogenes aureus was isolated. From only 1 patient, in whom fatal pneumonia developed later, was a streptococcus isolated. The author explains the difference in the type of bacterium causing the complications in the two epidemics as due to the different original environments of the people involved. The first year the patients came from the rural areas of Poland, whereas in the second year they came from more populated areas of Bessarabia. More resistance to streptococcic infections is exhibited by persons from urban communities than by those from rural areas.

BRAHDY, Mount Vernon, N. Y.

Acute Infectious Diseases

TULAREMIA. T. K. LAWLESS, Arch. Dermat. & Syph. **44**:147 (Aug.) 1941.

Lawless gives a résumé of the historical, clinical and diagnostic measures for the identification of a tularemic infection.

An antigen made from necrosing glands is offered as an aid to the early diagnosis.

Descriptions of the histologic pictures of an early ulcer, a subacute ulcer, a lymphatic gland and the site of an antigen reaction are given.

A review of the treatment is given, and the author states his intention to report later on the value of the tularemic antigen as a therapeutic agent.

JACKSON, Iowa City.

RAT-BITE FEVER IN AN INFANT BITTEN AT THE AGE OF ELEVEN DAYS. JOSEPH GREENGARD AND EDMOND R. HESS, J. A. M. A. **116**:2393 (May 24) 1941.

The authors report a case in which the diagnosis was proved by isolation of the spirochete.

HEERSMA, Kalamazoo, Mich.

RHEUMATIC FEVER IN CHILDHOOD. EDWARD F. BLAND, New England J. Med. **224**:629 (April 10) 1941.

Bland states that there is now general agreement that it is important to protect the hearts of children with rheumatic fever by rest in bed, not only during the relatively short acute phase of the disease but throughout the illness, until all evidence of rheumatic activity has subsided.

Children between 5 and 15 years of age with rheumatic fever were accepted from the wards and clinics of the Massachusetts General Hospital for convalescent care. Medical social workers have kept in touch with each patient at frequent intervals. All children were visited by the physician in charge at monthly intervals, and oftener in special cases. These patients ultimately required the aid of certain minimal laboratory guides—the most helpful of which was the determination of the sedimentation rate of the red blood cells. After all evidence of infection had subsided, these patients were allowed out of bed; the time was increased an hour a week, and at the end of four or five weeks they returned to the outpatient clinic.

Following this general plan, the examiners studied 64 patients. For 26 children, or 48 per cent of the 54 patients with the disease in the active stage, ward care in the general hospital was necessary during the more acute stage of the disease.

Two admissions to the hospital were necessary for 6 patients, and 1 patient was admitted three times. The average stay in the ward was four weeks.

The duration of recognized rheumatic activity in this group of 54 children averaged eight months for each patient. Seventeen (one third) of the 54 patients of the group had severe rheumatic fever; in 26 (one half) the rheumatic fever was moderately severe, and in the remaining 11 (one fifth) it was mild. No pure chorea occurred in the group of children studied.

In contrast, there were at the House of the Good Samaritan from 1934 through 1939 a total of 615 patients of essentially the same age as that of the patients in the five year study who also received protracted bed care and even closer medical supervision.

A comparison of the mortality figures for the two groups revealed that in the smaller series of patients 6 died as a result of congestive failure, all necessarily from the group of 39 with heart disease; this gave a mortality of 15 per cent. From the larger series of 387 patients with heart disease, 119 died—a mortality of 30 per cent, or twice as high as that in the smaller series. The results of this special study indicate that approximately 20 per cent of the patients, (and this includes those with severe cardiac involvement) ideally require institutional care for many months. For the remaining 80 per cent, care in a foster home or supervised care in the patient's own home seems adequate.

The daily cost of the three types of bed care for a child with rheumatic fever in Boston is approximately as follows: at Massachusetts General Hospital, $7.50; at the House of the Good Samaritan, $3.50, and in foster homes, $1.90. The expense involved in the patient's own home is largely indeterminate and necessarily variable.

GENGENBACH, Denver.

A MEDICAL-SOCIAL PROGRAM FOR THE CHILD WITH RHEUMATIC FEVER. EDITH M. TERRY, New England J. Med. **224**:632 (April 10) 1941.

Terry reports that the medical-social program for children with rheumatic fever at the Massachusetts General Hospital was instituted some thirty years previously under the direction of Dr. Fritz B. Talbot. Dr. Talbot outlined the following as essential for the adequate care of the child with cardiac disease: hospital care for the acutely ill child; supervision of subsequent bed care at home; provision for amusement; convalescent homes; vocational guidance, and prolonged medical and social service supervision.

The following is an outline of the methods employed and the resources available in Boston: (1) medical and social aspects, including hospitalization, placement in medical foster homes, medical-social home care, nursing care at home, medical-social case work, and consistent follow-up; (2) educational aids, including cooperation of home teachers, tutoring by college students, cardiac summer school, school nurses, and the Mothers' Club; (3) recreational facilities including the In-Bed Club, with its membership of children facing like restrictions, and occupational therapy.

As a means toward this end a working team was appointed. This group consisted of a physician in charge of the medical aspects, a medical-social worker from the clinic, a social worker, who was added to the staff of the child-placing agency, and an occupational therapeutist. A further role of the clinic worker was to act in liaison between physician, child-placing agency and hospital.

GENGENBACH, Denver.

SOME EFFECTS OF EXPERIMENTAL TRICHINOSIS IN THE DOG. EDGAR H. BEAHM and MYRON N. JORGENSEN, Proc. Soc. Exper. Biol. & Med. **47**:294 (June) 1941.

Thirteen mature dogs were infected by feeding 90,000 to 480,000 trichina larvae contained in fresh rabbit muscle, and determinations of the hemoglobin, calcium and inorganic phosphate contents of the serum as well as cytologic determinations

were made. All animals exhibited gradual increase in the number of eosinophils, which reached a maximum in ten to fifteen days. Increase in the serum calcium was observed in only 4 instances, and in these a massive infection had occurred.

HANSEN, Minneapolis.

EXPERIMENTS ON IMMUNIZATION OF HUMAN BEINGS AGAINST INFLUENZA A. WALTER P. MARTIN and MONEOR D. EATON, Proc. Soc. Exper. Biol. & Med. **47**:405 (June) 1941.

In two large institutions, X and Y, 416 of 4,976 subjects and 413 of 2,900 were vaccinated with living virus and complex formaldehyde-treated vaccine prior to an outbreak of so-called influenza. Complement fixation tests disclosed the presence of influenza A. There appeared to be some protective effect in one institution but not in the other. No difference in the efficiency of the two types of vaccine was noted in these studies.

HANSEN, Minneapolis.

RHEUMATISM IN CHILDHOOD AND ADOLESCENCE. P. KUTUMBIAH, Indian J. Pediat. **8**:65 (April) 1941.

In the opinion of this author the long-standing belief that rheumatism does not occur in tropical climates is not justified, as he finds the incidence in Ceylon nearly as high as in England and in this country. No studies have been made to show the incidence among Europeans living in the tropics and among Indians in temperate climates, but it is doubtful if race is a factor in causing rheumatism. The greatest number of cases are found in the age group between 16 and 20; but if accurate histories were available, many of these would undoubtedly be moved down to the 13 to 15 group. Rheumatic infection is found to attack females more often that males, but the incidence among males was higher than suspected. No familial factor can be shown, nor is there any evidence of communicability. No definite decision as to whether the conditions of temperature, rainfall and humidity have any marked influence on the incidence of rheumatic infection in the tropics can be arrived at. Contrary to opinions from other parts of the world, rheumatic infection is more prevalent in the upper middle class than in the very poor; it is more definitely prevalent in urban communities; it is more prevalent in children attending school than in those who do not. There is no correlation with diet and nutrition. Damp and cold have no effect on the incidence of rheumatic infection except as they influence the prevalence of infection of the respiratory tract.

TENNEY, Madison, Wis.

Chronic Infectious Diseases

STUDIES ON THE ROLE OF SPIROCHAETA PALLIDA IN THE WASSERMANN REACTION. 1. COMPLEMENT FIXATION IN SYPHILIS, LEPROSY, AND MALARIA WITH SPIROCHETAL ANTIGENS. JOHN A. KOLMER, CLARA C. KAST and ELSA R. LYNCH, Am. J. Syph., Gonor. & Ven. Dis. **25**:300 (May) 1941.

Because of the different percentages of positive complement fixation reactions for syphilis, investigation was started with various types of antigen on serums of patients having several different diseases. The authors state that they believe that in syphilis, leprosy and malaria a complement-fixing antibody is to be found in the serum for the antigen of alleged cultures of Spirochaeta pallida but that this is a group antibody capable of fixing complement with antigens of Spirochaeta macrodentium and Spirochaeta microdentium. They state that even normal serum contains this natural antibody and that it plays a large part in the mechanism of complement fixation with antigens of alleged cultures of S. pallida. They believe that the presence of this group spirochetal antibody is responsible for the high percentage of the nonspecific reactions in syphilis and that these can be avoided

by using a sufficiently small amount of antigen. The conclusions that the authors reach are as follows:

"1. A large percentage of normal nonsyphilitic sera (to a lesser extent cerebrospinal fluids) contain a natural spirochetal complement-fixing antibody, especially for S. microdentium.

"2. This is a group antibody capable of fixing complement with antigens of alleged cultures of S. pallida.

"3. In syphilis, leprosy and malaria there is apparently produced some increase of spirochetal complement-fixing antibody.

"4. But the presence of the natural antibody results in such a large percentage of nonspecific complement fixation reactions with antigens of S. pallida as to render it probable that spirochetal antigens are inferior to alcoholic tissue extracts re-enforced with cholesterol as antigen for the Wassermann test."

ROYSTER, University, Virginia.

PREVENTION OF TRANSFUSION SYPHILIS. F. J. EICHENLAUB, ROBERT STOLAR and ALVIN WODE, Arch. Dermat. & Syph. **44**:441 (Sept.) 1941.

As the result of their experiments, the authors believe that the addition of 0.01 Gm. of mapharsen to the sodium citrate solution for each 500 cc. of blood will prevent the infection of recipients even though the donor has syphilis. They believe, therefore, that this measure may replace the routine checking of donors by Wassermann tests. If this method is not used routinely, it should always be used when time to investigate the donor for syphilis is too short or when any doubt as to the donor's freedom from syphilis exists. JACKSON, Iowa City.

CLINICAL STUDIES ON THE HARMLESSNESS OF AND TUBERCULIN REACTIVITY FOLLOWING BCG VACCINATION BY THE MULTIPLE PUNCTURE METHOD. SOL ROY ROSENTHAL and IRWIN S. NEIMAN, J. Pediat. **19**:16 (July) 1941.

The subcutaneous or intradermal injection of BCG results frequently in draining cold abscesses and suppurating local lymph nodes. In order to overcome these complications a new method for vaccination (multiple puncture) was used in 258 newborn infants vaccinated on the third to the tenth day of life. The results obtained from this method of vaccination are presented. A comparison of the multiple puncture and intradermal methods of vaccination revealed that the former is simpler in application and yields fewer complications. The reactivities to tuberculin following both methods of administration are comparable.

RAUH, Cincinnati.

ANTITUBERCULOUS VACCINATION WITH BCG. J.-A. BAUDOUIN, Union méd. du Canada **70**:750 (July) 1941.

Forty-four thousand seven hundred and thirty-four vaccinations with BCG had been given to the date of writing this article (January 1941). The infants had not received any further protection (the Maternal Assistance BCG Clinic institutionalizes their babies four months), and yet the mortality rate from tuberculosis was remarkably lower than in a control group. In fact, the general mortality rate was lower than in the unvaccinated group. DAFFINEE, Boston.

TUBERCULOMA OF THE EYE. G. E. DODDS, Brit. J. Ophth. **25**:384 (Aug.) 1941.

The patient was a Yoruba boy 12 years of age. The globe, completely involved, was greatly enlarged. There was advanced spinal caries with spastic paralysis of the lower extremities. After three months of treatment the patient's general health had improved and the tumor of the eye diminished in size. The eyeball was enucleated. A soft solid mass which bore no resemblance to an eyeball except for

a remnant of the lens and cornea, it consisted of necrotic tissue bathed in creamy, yellow pus. Microscopically it was a mass of caseous tissue in which were numerous typical tuberculous giant cells. Direct smears failed to reveal tubercle bacilli, but a guinea pig inoculated with pus from the eye and killed after seven weeks showed typical tuberculous lesions containing acid-fast bacilli.

W. ZENTMAYER [ARCH. OPHTH.].

RADIOGRAPHIC APPEARANCES OF "PRECLINICAL" TUBERCULOSIS. GWEN HILTON, Tubercle **22**:135 (June) 1941.

The correct interpretation of abnormal shadows in the lungs of apparently normal subjects not only requires skill and judgment on the part of the physician but may mean, from the subjects' standpoint, either arrest or full development of serious disease. In the present state of knowledge shadows persisting for three months should be considered as having great significance and should be followed roentgenographically at monthly intervals.

The opacities observed in the routine examination of 417 medical students were divided into two categories, pulmonary "coin" shadows and pulmonary "fluffy" shadows. The "coin" shadows were rounded and clearcut, frequently with slightly increased linear markings leading to the hilus. The "fluffy" shadows were soft and homogeneous, with well defined edges but with an irregular outline. From these also linear markings may extend to the hilus. The significance of these shadows is determined only by subsequent roentgen follow-up examinations. Similar shadows may result from pneumonitis or small areas of collapse, but these usually clear up in a few weeks. It is of great importance that the roentgenographic technic should be as nearly perfect as possible, and it is of special importance that all films of the same subject should be comparable. Case histories and excellent plates accompany this article. EUGENE SMITH, Ogden, Utah.

THE WELTMANN REACTION IN TUBERCULOUS PLEURITIS AND EMPYEMA IN CHILDREN. T. KIKUCHI, Acta pediat. japon. **47**:434 (April) 1941.

The author made determinations of the Weltmann reaction in 37 children with tuberculous pleurisy, 5 patients with empyema and 20 normal subjects, using both serum and cerebrospinal fluid as test materials. Whereas the Weltmann reaction with normal serum usually ranged from 0.5 to 0.4 per cent, it was invariably shortened in tuberculous pleuritis, returning to the normal range with recovery. In patients with empyema the reaction was shortened during the acute stage, even to a greater degree than that seen in tuberculous patients, but with clinical improvement it returned to the normal value. The exudative fluids obtained by pleural puncture usually gave shorter coagulation bands than the serum in tuberculosis with no complications. In 7 cases of bilateral pleuritis, it was found that the Weltmann reaction frequently showed varying ranges of coagulation, the more recently affected side always showing a shortening of the band. The Weltmann reaction of transudates was entirely negative. KATO, Chicago.

Diseases of Blood, Heart and Blood Vessels and Spleen

DEATH FROM TRANSFUSION OF PLASMA. FRANK MAYNER, J. A. M. A. **116**:2014 (May 3) 1941.

A patient, 4 years old, was given a transfusion of his father's blood during the course of treatment for a nephrotic syndrome. During a recurrence two and one-half months later he was given a transfusion of plasma from the father. Death occurred as a result of anoxemia following precipitation of fibrin in the pulmonary artery system. HEERSMA, Kalamazoo, Mich.

COMPARATIVE EFFECTS OF SULFONAMIDE COMPOUNDS AS TO ANEMIA AND CYANOSIS. ARTHUR P. RICHARDSON, J. Pharmacol. & Exper. Therap. **72**:99 (May) 1941.

As blood complications, anemia and cyanosis are the most common and serious accidents in the use of sulfonamide compounds. This study was made on white mice. The drugs were given in a food, which resulted in a fairly uniform concentration in the blood. It was found that on a basis of intake the drugs were injurious in the following ratio: sulfanilamide was 2.1 times as injurious as sulfapyridine, 4.3 times as injurious as sulfathiazole and 10.9 times as injurious as sulfanilylguanidine. However, when corrections were made for differences in absorption, excretion, molecular weight and partition between erythrocytes and plasma, all four compounds were of the same order of injuriousness. Cyanosis, characterized by sulfhemoglobinemia, was observed only with higher doses of sulfanilamide and sulfapyridine.

PILCHER, Cleveland.

RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF BLOOD DISORDERS IN INFANCY AND CHILDHOOD. CARL H. SMITH, M. Clin. North America **25**:659 (May) 1941.

The mode of action and the practical application of vitamin K in hypoprothrombinemia are briefly discussed. The principal indication for the use of this substance in infancy is in the prevention and treatment of hemorrhagic disease of the newborn. Its use is also suggested in cases of intracranial hemorrhage, since the physiologic hypoprothrombinemia of the newborn may contribute to the persistence of the bleeding.

The examination of bone marrow obtained by sternal puncture may give early and important diagnostic information otherwise not obtainable. In the detection of the toxic effects of sulfanilamide and its derivatives, especially on the myeloid elements of the blood, examination of the bone marrow reveals the extent of the damage to the mature granulocytes and their precursors at first hand. The toxic effects of these drugs on the bone marrow are revealed by varying degrees of suppression of the granulocytic elements and at times by a diminished total cell count. The occurrence of the latter in children may be regarded as a caution signal.

In the differentiation of purpuric states and as a guide to splenectomy, information of great value may be obtained from study of the bone marrow. In essential thrombopenic purpura, hyperplasia of the megakarycytes appears to be the usual finding. Reduction to more normal levels occurs after splenectomy. In cases of purpura characterized by megakaryocytic aplasia splenectomy is contraindicated.

Roentgenograms of the skeletal system may furnish valuable diagnostic evidence with certain blood dyscrasias. This is especially true when they occur in infants and young children, in whom bone changes are more rapid and characteristic hematologic features may be absent. In childhood leukemia extensive involvement of the bone marrow may antedate for a considerable period the development of physical signs and changes in the blood. The roentgenogram, however, may reveal generalized or local rarefaction, focal areas of bone absorption and periosteal elevation. Various bone changes are also found in erythroblastic anemia, hemolytic jaundice and sickle cell anemia.

Recently attention has been called to certain peculiar cells occurring in Cooley's anemia. One, the so-called "target cell," is a macrocytic cell having a deeply stained center and a periphery arranged in light and dark zones. A more characteristic cell is the "large pale erythrocyte," which contains irregularly distributed clumped hemoglobin and whose intervening areas seem to possess staining defects.

EUGENE SMITH, Ogden, Utah.

THE CONVALESCENT CARE OF CHILDREN WITH HEART DISEASE DUE TO RHEUMATIC FEVER. PAUL D. WHITE, New England J. Med. **224**:627 (April 10) 1941.

This is the first of three articles pertaining to a joint five year study of the problem of the care of children with rheumatic heart disease by the Children's

Mission to Children, the Children's Cardiac Clinic at the Massachusetts General Hospital and the Committee for the Home Care of Children with Heart Disease. This study began in 1934 and ended in 1939. The aim was twofold: to determine the value of the relatively intensive care of these children and to ascertain the best way to utilize the resources available for such care.

The chief lesson learned from the study was that long and adequate bed care for children with acute rheumatism or acute rheumatic heart disease is best carried out when the environment is most carefully arranged and homelike, when provision is made for intelligent nursing, expert and readily available medical attention, food adequate in calories and vitamins and protection against colds and when effective measures in the form of recreational and occupational therapy have been instituted to secure and to hold the cooperation of the children themselves. Equally significant is the vital contribution of bringing expert medical attention, in addition to social service, to the children's own homes and to the foster homes, a serious omission in the past. Still another vital need is the protection of the child from colds, which are by far the commonest and most serious cause of exacerbations in cases of subacute or quiescent rheumatic fever.

The morale and education of the children, important factors in securing the cooperation of both children and parents in the treatment, have been maintained at a high level during this study, and excellent results have been obtained.

GENGENBACH, Denver.

DETERMINATION OF PANTOTHENIC ACID IN NORMAL BLOOD AND URINE BY MICROBIOLOGICAL TECHNIC. MICHAEL J. PELCZAR JR. and J. R. PORTER, Proc. Soc. Exper. Biol. & Med. **47**:3 (May) 1941.

It is possible to assay the content of pantothenic acid of tissues by placing aqueous extracts in mediums and noting the growth response of the bacterium Proteus morganii. Study of the blood of 17 normal persons disclosed the pantothenate content to average 0.059 micrograms per cubic centimeter (range 0.030 to 0.099 micrograms). The average amount of pantothenic acid in twenty-four hour urine excretions of 9 persons was 3.81 mg. (1.46 to 6.79 mg.).

HANSEN, Minneapolis.

MALIGNANT HYPERTENSION IN CHILDHOOD. DONALD COURT, Arch. Dis. Childhood **16**:132 (June) 1941.

Malignant hypertension may be defined as a progressive generalized vascular disorder associated with gross hypertension, in which renal dysfunction is a secondary and late manifestation. The clinical features of headache, vomiting, papilledema and visual disturbance are associated with severe and progressive hypertension for which no cause can be found. A full description of the condition in a child of 10 years is given.

KELLY, Milwaukee.

A CASE OF AGRANULOCYTOSIS IN AN INFANT: RECOVERY. H. CECIL BARLOW, Brit. M. J. **1**:669 (May 3) 1941.

In this article the author reports a case of agranulocytosis in a girl 23 months old. She was first seen with a pain in the left knee, which was treated with sodium salicylate. Later there developed an infection of the upper respiratory tract and otitis media of the right ear, which was treated with sulfapyridine. The child was anemic before being treated with sulfapyridine, and she became seriously sick; on entering the hospital she had a red blood cell count of 930,000 and a hemoglobin content of 18 per cent.

The child was treated with two large transfusions, of 500 cc. and 250 cc., intravenously. In addition she was given pentnucleotide twice a day. The child responded nicely to blood transfusions, although the smear revealed a drop in the percentage of polymorphonuclear cells. On the eighth day of treatment with

pentnucleotide she finally acquired a polymorphonuclear leukocytosis, and her resistance to infection and recovery coincided with this rise in the blood picture. The author states that the blood picture suggested aleukemic lymphatic leukemia. It was thought this might be secondary to an idiosyncrasy to sulfapyridine.

ROYSTER, University, Virginia.

MORBID RED CELL DEVELOPMENT AND THE TREATMENT OF ANEMIA. M. C. G. ISRAELS, Lancet **2**:207 (Aug. 23) 1941.

A scheme of normal and pathologic erythropoiesis is proposed which shows that disease may cause changes in the development of the normoblastic group of cells, or maturation may be deflected to a megaloblastic group—regarded by some as a return to the first type of embryonic blood cell development.

Four main groups of pathologic erythropoiesis are distinguished:

1. Failure of maturation of proerythroblasts with suppression of normoblast development and hyperplasia of megaloblasts.

2. Failure of maturation of normoblasts with hyperplastic but distorted development of normoblasts, leading to the formation of inadequately hemoglobinized microcytes.

3. Hyperplastic normal maturation, which if sufficiently severe and prolonged leads to the appearance of many early erythroblasts and unusually early formation of hemoglobin in the normoblasts.

4. General failure of erythropoiesis, with decrease or absence of erythroblasts (when present, all normoblasts).

In group 1 are included pernicious and allied anemias due to deficiency or disturbed action of the hemopoietic liver principle; group 2 corresponds to the iron deficiency anemias; group 3 changes are found in a variety of anemias characterized by vigorous erythropoietic response to loss of red blood cells—hepatic deficiency plays no part here; group 4 comprises the idiopathic and secondary aplastic anemias.

Treatment varies according to the pathologic group. Specific liver or desiccated stomach treatment is appropriate only for groups 1 and 3.

LANGMANN, New York.

FAMILIAL EOSINOPHILIA. Y. HIRO and S. TASAKA, Acta pediat. japon. **47**:604 (May) 1941.

The authors report observations on 2 families, in one of which eosinophilia of unexplained origin occurred in all members and in the other of which it occurred in all but 1 member. In the latter family the father had from 10 to 13.5 per cent eosinophils, the mother 15.5 per cent, the first child 17 per cent, the second child 12.5 per cent, the third child from 5 to 25 per cent and the fourth child 18 per cent. The fifth child was the only member of this family to have a normal eosinophil count (4.5 per cent). In the former family, the percentages of eosinophils were as follows: father, 17; mother, 13.5; first sibling, 8, and third sibling, from 19.5 to 36. The second and fourth pregnancies in this family terminated in miscarriages. In each case individually the authors endeavored to ascertain the cause or causes of the eosinophilia, but the only suggestive finding was the discovery on one occasion only of a few ascarids (Ascins ovis) in the stool of the mother in the first family. The otherwise completely negative findings led the authors to regard these as cases of familial eosinophilia.

KATO, Chicago.

THE GROS REACTION IN CHILDREN. N. NAKAYAMA, Acta pediat. japon. **47**:700 (June) 1941.

Nakayama made observations on the turbidity and precipitation reaction of both normal and abnormal serums by adding increasing amounts of Hayem's

solution, the reaction following which he proposed to designate as the Gros reaction. A positive reaction of first degree (addition of 3 to 5 drops of Hayem's solution to 0.5 cc. of serum) occurs in serums of persons with such diseases as tuberculosis, nephritis, catarrhal jaundice and scarlet fever; but in serums of healthy persons the reaction is entirely negative. There appears to be a correlation between the Gros reaction and the Takata-Ara reaction, both of which are frequently positive in cases of increased erythrocyte sedimentation rate.

KATO, Chicago.

Diseases of Nose, Throat and Ear

ACUTE LARYNGOTRACHEOBRONCHITIS: ANALYSIS OF SIXTY-TWO CASES WITH REPORT OF AUTOPSIES IN EIGHT CASES. HORACE O. BELL, HENRY BOYLAN ORTON, ELLIS L. SMITH and RALPH A. FORD, Arch. Otolaryng. **33**:926 (June) 1941.

A survey of 62 cases of acute laryngotracheobronchitis and reports of 8 autopsies are presented. Clinical pictures, differential diagnoses and treatment are discussed; terms are defined, and the relative merits of intubation and tracheotomy are analyzed.

GREENWOOD, Chicago.

INVOLVEMENT OF THE JAW JOINT IN ACUTE SUPPURATIVE OTITIS MEDIA. GEORGE E. SHAMBAUGH JR., Arch. Otolaryng. **33**:975 (June) 1941.

Attention is called to the rarity of infection extending from the middle ear to the jaw joint when the close proximity of the mandibular fossa to the middle ear is taken into consideration. Adding 3 cases of his own experience to 2 of Volger's, previously reported in 1923, the author presents eight important diagnostic criteria based on clinical and roentgen observations, discusses three possible ways in which involvement of the jaw might result from an aural infection, and outlines as treatment surgical drainage without opening of the joint capsule.

GREENWOOD, Chicago.

VOWEL ELEMENTS IN THE CRYING VOCALIZATION OF INFANTS UNDER TEN DAYS OF AGE. ORVIS C. IRWIN and THAYER CURRY, Child Development **12**:99 (June) 1941.

Forty infants, 20 boys and 20 girls, under 10 days of age were used for the purpose of studying the vowel sound equipment of newborn babies. Vocalization was entirely of a crying nature. The vowel elements appearing on each of twenty-five respirations were transcribed in the symbols of the International Phonetic Alphabet simultaneously and independently by two observers. A total of 1,000 respirations constitutes the data of the study.

It was found that: 1. The time sampling method is inadequate. 2. A behavior unit method (the single respiration) of observation enables the observer to transcribe easily such sounds as occur during the unit. 3. Agreement between observers averages 85 per cent and in certain situations is well over 90 per cent. 4. Only four vowels occur with appreciable frequency in the vocalization of newborn children: I, ɛ, æ and ʌ. 5. The most frequently used vowel element in the vocalization of newborn infants is the sound æ. It is the only vowel sound formed by all 40 babies. 6. Front vowels are more frequently used than middle and back vowels. 7. Among the front vowels the I and ɛ sounds are least used. 8. Back vowels are almost entirely absent. 9. There are no sex differences in the use of vowels. 10. There are no age differences within the period studied. 11. A comparison of these data with data in vowel usage in adult speech reveals striking differences.

It is inferred from these data that the course of development during infancy in the use of vowel sounds is the increasing use of back vowels.

FROM THE AUTHORS' SUMMARY.

THE PROFILE AS A VISUAL DEVICE FOR INDICATING CENTRAL TENDENCIES IN SPEECH DATA. ORVIS C. IRWIN, Child Development **12**:111 (June) 1941.

In this article is described a graphic method for the simultaneous presentation of a number of central tendencies in speech sound data. It consists of a profile of the relative frequencies of speech elements or categories of elements. Its construction consists of a simple modification of the principle of the bar graph. A series of equidistant points is laid off on an x axis from which perpendiculars may be erected to accommodate bars which signify the frequencies of various elements. The y axis is taken to represent per cents of frequency. The units of both axes are arbitrarily chosen, but for comparative purposes each should be kept equal from profile to profile.

The essential condition for the usefulness of this device is the establishment of equal total areas under each of the compared profiles. The total area is taken as 100 per cent and represents the total frequencies of all sounds in each of the compared sets of elements. Thus the frequency of each speech element under the profile is in turn an area which represents its proportional part of 100 per cent. Under these conditions the profile pattern will reveal readily the overall similarities and differences existing among groups of data.

Such a profile has much to commend it as a graphic presentation of the central tendencies of speech sound data, but it is not without its limitations, the greatest of which is the fact that it does not indicate variability within the individual category.

The article is concerned largely with a number of illustrations of the adaptability and use of the device. These illustrations are based on data which have been transcribed from the vocalization of newborn infants, of infants at several ages up to 2 years, of a group of low grade feebleminded children under 5 years and from a study of the distribution of elements in adult speech.

FROM THE AUTHOR'S SUMMARY.

SINUSITIS IN CHILDHOOD. J. VAILLANCOURT, Union méd. du Canada **70**:352 (April) 1941.

The ethmoid sinus is the most important sinus in young infants. The remaining sinuses do not develop until later childhood. In many cases chronic nasal discharge, cough, loss of weight and repeated colds are due to sinusitis and not to adenoidal vegetations.

DAFFINÉE, Boston.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

ANOTHER OUTBREAK OF GASTROENTERITIS FOLLOWING CONSUMPTION OF CREAMED-FILLED PASTRIES. Health News **18**:72 (May 5) 1941.

Twenty-eight cases of severe gastroenteritis were traced to custard-filled cream puffs. Such custard is an excellent medium for the development of bacteria. To avoid infection the filling should be used immediately after being prepared, and the filled shells should be properly refrigerated until consumed. Rebaking might reduce the incidence of poisoning.

AIKMAN, Rochester, N. Y.

BACILLUS MORGANI, TYPE I, IN ENTEROCOLITIS OF INFANTS. ERWIN NETER and NORMAN C. BENDER, J. Pediat. **19**:53 (July) 1941.

Six cases of acute enterocolitis in infants are described. From the stools of these patients Morgan's bacillus, type I, but none of the recognized enteric pathogens was isolated. A seventh patient, with a negative stool culture, was included because of circumstantial evidence of infection with this organism. Six of the infants ranged in age from 6 weeks to 7 months. Four of the patients died. The postmortem examinations revealed severe pseudomembranous enterocolitis in 3 cases and catarrhal enterocolitis in 1 case. Two of the patients were

twins, and their mother was found to harbor Morgan's bacillus type I in her intestinal canal. One patient harbored this organism for weeks after complete recovery. The incidence of Morgan bacilli and other doubtful enteric pathogens in the feces of children with diarrhea is discussed. Of 54 specimens of feces from children with diarrhea which contained enteric bacilli other than Bacillus coli and Bacillus aerogenes, 22 showed recognized enteric pathogens, while 32 contained doubtful enteric pathogens (Morgan's bacillus types I, X, XII and XIV, Bacillus alkalescens, Bacillus proteus, Bacillus pyocyaneus and Bacillus coli anaerogenes). The authors stress the necessity of careful bacteriologic studies of all organisms in cases of enterocolitis to determine the incidence of the "doubtful pathogenic" members of the enteric group of micro-organisms and to elucidate further the relation of these organisms to enteric disease. RAUH, Cincinnati.

CONGENITAL ATRESIA OF THE ESOPHAGUS WITH TRACHEOESOPHAGEAL FISTULA: REPORT OF A SUCCESSFUL EXTRAPLEURAL LIGATION OF FISTULOUS COMMUNICATION AND CERVICAL ESOPHAGOSTOMY. N. LOGAN LEVEN, J. Thoracic Surg. **10**:648 (Aug.) 1941.

The author reports the surgical treatment of congenital atresia of the esophagus with tracheoesophageal fistula in an infant, who at the time of publication of the report had reached the age of 1 year and 7 days. He discusses the previous attempts at correction of this deformity, all of which have met with uniformly unsuccessful results at the hands of the most competent surgeons. From previous experience with gastrostomy in the care of infants with such anomalies the author decided that direct attack on the fistulous communication is necessary.

After careful preparation, the infant was gastrostomized, and between this procedure and the next a catheter was kept leading into the jejunum through the pylorus. The mouth was frequently aspirated of mucus. Through an extrapleural approach with resection of the right fourth rib, the fistulous communication between the trachea and the esophagus was doubly ligated with silk, after the azygos vein had been ligated and divided. Two and one-half months later, the blind proximal pouch of esophagus was brought out through a left cervical incision. This was connected with the gastrostomy opening. An antethoracic esophagoplasty is contemplated for the future to reestablish continuity. This is a remarkable case report.

DORSEY, Chicago.

STEATORRHOEA IN INFANCY. HELEN DEEM and MURRAY MCGEORGE, New Zealand M. J. **40**:155 (June) 1941.

Seven cases of steatorrhea in infancy, probably due to congenital pancreatic defect, are described. The cases were remarkably similar in regard to the following elements: (1) early age at onset; (2) poor progress, even though the children were receiving their theoretic caloric requirements; (3) the stools typically steatorrheic in type; (4) improvement of the babies as soon as a fat-free or reduced fat diet was substituted (a further improvement was noted in two instances in which pancreatin also was used); (5) a tendency of all the infants to acquire infections of the respiratory tract (4 in the series died, 2 probably from respiratory disease).

WEIGAND, Indianapolis.

Nervous Diseases

NEURAL MATURATION OF THE INFANT AS EXEMPLIFIED IN THE RIGHTING REFLEX, OR ROLLING FROM A DORSAL TO A PRONE POSITION. MYRTLE B. MCGRAW, J. Pediat. **18**:385 (March) 1941.

Neuromuscular changes as exhibited by 75 infants in the achievement of ability to turn from a supine to a prone position have been described. A total of 1,840 observations have been rated in accordance with criteria which differentiate four

significant phases. The group data are supplemented by longitudinal data on 4 individual infants. Curves showing the age period when each phase is the characteristic mode of behavior are presented. Changes in the pattern of behavior as they reflect the "righting reflexes" described by Magnus have been discussed. It has been suggested that the rolling response is perhaps in the infant a phyletic activity which becomes integrated at a nuclear level before cortical dominance occurs. Subsequently, it is utilized as a component of the human righting response, i. e. the assumption of an erect posture. As the latter behavior matures, the rolling-over phase tends to become eliminated or at least diminished.

RAUL, Cincinnati [AUTHOR'S SUMMARY].

SPONTANEOUS SUBARACHNOID HEMORRHAGE. C. T. TURNER, South. M. J. **34**:949 (Sept.) 1941.

Turner states that spontaneous subarachnoid hemorrhage may result from a number of different conditions. It constitutes a frequent type of vascular accident in young adults and children. In elderly people it is practically always the result of atherosclerotic changes in the blood vessels composing the intracranial arterial system.

In children, subarachnoid hemorrhage is usually an extravasation of blood over the vertex of the brain and is associated with blood dyscrasias. In newborn babies, these hemorrhages occur in evident absence of vitamin K.

In young adults, spontaneous subarachnoid hemorrhage most frequently results from a ruptured aneurysm. These aneurysms occur near sharp bends or at the bifurcations of the arteries.

Intracranial aneurysms probably exist more frequently than they are suspected. They rarely attain sufficient size to produce neurologic signs.

Aneurysms of the internal carotid artery may produce paralysis of one or more of the extrinsic muscles of the eye.

Spontaneous subarachnoid hemorrhages associated with any condition are related to a psychophysiologic factor, resulting in emotional tension or effort.

Albuminuria is often found in cases of ruptured aneurysm.

SCHLUTZ, Chicago.

COMBINED FORMS OF MENINGITIS: MIXED INFECTION OF THE MENINGES BY THE TUBERCLE BACILLUS AND MENINGOCOCCUS. JACK FIDDES, Arch. Dis. Childhood **16**:140 (June) 1941.

A case of combined tuberculous and meningococcic meningitis in a child of 14 months is described. The order in which the infections occurred can be surmised from the postmortem examination. The primary tuberculous focus in the lung, which was fibrotic, was presumably acquired some months before, perhaps from the grandfather, and the onset of the tuberculous meningitis was, no doubt, six weeks before the child was seen at the hospital, when a change was first noticed. The intracranial tuberculosis must have been present for some time, judging by the tuberculomas in the substance of the brain and the many miliary tubercles on the surface. The child might have been a carrier of the meningococcus in the throat, and presumably this organism became sufficiently virulent to cause meningitis only about a week before the patient was admitted to the hospital.

Two other unusual aspects of the case were: (1) that the pus in the cerebrospinal fluid from the postbasic suppurative type of meningitis increased greatly just before death, in spite of the fact that the sulfapyridine had not been withdrawn; (2) that the opisthotonos, or "gun-hammer" position, was of extreme severity and was sustained for a long time.

KELLY, Milwaukee.

A Disease of Animals Transmitted to Human Beings. M. Panisset, Union méd. du Canada **70**:597 (June) 1941.

This is a résumé of knowledge to date concerning equine encephalomyelitis.

Daffinée, Boston.

Psychology and Psychiatry

Quantitative Studies in the Development of Erect Locomotion. Myrtle B. McGraw and Kenneth Breeze, Child Development **12**:267 (Sept.) 1941.

The present investigation was undertaken for the purpose of obtaining numerical values for certain aspects of a developing behavior phenomenon. The function studied was development of erect locomotion. A method was adopted whereby a picture of the child walking and an impression of the footprints could be photographed on the same 16 mm. film. Counting the number of frames involved in the movement of each foot provided a measure of temporal changes as increasing integration was achieved. Frame by frame projection and plotted curves of the path of the body through space yielded numerical values for certain spatial factors involved. When such values, obtained at successive intervals for the same children, were plotted against chronologic age, curves showing improvement in the efficiency of walking were available. Since the measurements which could be taken from the films were numerous, it was necessary to select a few most indicative ones. Therefore an index of efficiency was defined as the ratio between the horizontal distance covered during a step and the length of the path of the center of gravity of the lower leg. In the mature, well established gait, the amounts of time during a step when each foot is on the ground and when it is in the air tend to be equal, but in the unstable gait of the toddler the difference between the times is considerable. The rate at which the action time of the two feet approximate each other is evidence of the rate at which functional integration is being achieved. Although the method adopted was tedious, laborious and expensive, the measures obtained serve to demonstrate that quantitative values can be obtained for changing phenomena, for quantities which are often accepted as inherently qualitative. They serve further to support the thesis that the difference between qualitative and quantitative data is not contingent on some inherent difference in the nature of the phenomena.

Authors' Summary.

The Effects of Infant Feeding-Frustration upon Adult Hoarding in the Albino Rat. J. McV. Hunt, J. Abnorm. & Social Psychol. **36**:338 (July) 1941.

For a considerable time psychologists, psychiatrists, psychoanalysts and some anthropologists have attributed great importance to the experiences of infancy and childhood in determining the personal characteristics of adult life. This study was conducted to obtain controlled evidence concerning the claims of psychoanalysis that experiences during infancy can affect adult behavior.

It would be highly desirable from a scientific standpoint to rear human beings under controlled circumstances. Since such a condition is out of the question, for social and humanitarian reasons, one is left with the alternative of working with lower animals.

Feeding was chosen because it is the simplest factor to control in animal work. While food storing in rats is a long cry from stinginess and collecting in human beings, it is nicely measurable and can be produced at will with a relatively slight amount of food deprivation at any time.

The feeding frustration to which the experimental animal groups were subjected consisted of ten minute group feedings of wet mash at irregular intervals varying from nine to thirty-six hours for fifteen days. To minimize inanition, any animal failing to gain or falling in weight distinctly below its litter mates of the same sex was given extra individual feedings. Wet mash was available continuously in the cages of the controls.

Approximately five months after the end of the period of infantile feeding frustration the animals were segregated in individual cages of the hoarding apparatus. There they lived with food pellets continuously available for nine days to get them accustomed to the cages and to segregated life.

Both the experimental and the control animals were then supplied an unlimited quantity of food over a five month period. Then the experimental and the control groups—now adult rats—were subjected to a relative food famine. The object was to observe their reaction to food deprivation occurring during their maturity. After this period of food frustration in adult life they were supplied with an unlimited quantity of food pellets. Special apparatus permitted the experimenters to count the number of pellets which were hoarded by each animal.

The effect of infantile frustration on adult behavior was demonstrated by the fact that the experimental animals—those which had been frustrated in feeding at the earlier age of 24 days—hoarded more than two and a half times as many pellets as their litter mate controls, who had suffered no deprivation during their infancy.

The importance of the age at which the infantile frustration occurred is shown by the fact that another group of experimental animals in which the frustration during infancy was delayed for eight days did not resort to excessive hoarding after frustration in later life.

WISE, Howard, R. I. [ARCH. NEUROL. & PSYCHIAT.].

Diseases of the Genitourinary Tract

GLOMERULAR NEPHRITIS. HERBERT C. ARCHIBALD, Arch. Pediat. **58**:555 (Sept.) 1941.

Archibald analyzed 43 consecutive cases of glomerular nephritis in detail as to type of onset, physical observations, laboratory data, including Addis tests, and prognosis.

Of the 43 patients hospitalized, 33 have been followed in the clinic. In 26 the nephritis was postinfectious; in 7 it was not. Eighteen (70 per cent) of the first group recovered; in 4 (15 per cent) the condition became latent, and 4 (15 per cent) are dead. None of the group thought to have noninfectious forms of the disease have recovered; 1 has a degenerative form, 2 still have active nephritis and 4 are dead. In the clinic, complete follow-up over a long period of time was impossible. After three years from the onset, 9 patients were normal as judged by the Addis test and by clinical observations; 5 continued to have nephritis in a latent or active stage, and 5 had died.

The prognosis in this series of cases is neither as bad as that reported by Snoke from San Francisco nor as good as that reported by Boyle. The reason for the discrepancy in the reported cases is not known. However, the author concludes that glomerular nephritis in children is a serious disease in his geographic area.

ORR, Buffalo.

ENURESIS TREATED BY URETHRAL DILATATION. H. P. WINSBURY-WHITE, Lancet **2**:331 (Sept. 20) 1941.

Three hundred and ten cases of enuresis were analyzed and treated by the author. In 16 per cent there was a history of an infectious illness, usually an exanthem, immediately preceding the onset. In 49 per cent it began during infancy and in 84 per cent before the end of the sixth year. Sixty-one per cent of the patients were girls.

Enuresis in both sexes was commonly associated with chronic inflammatory changes in the posterior part of the urethra and at the neck of the bladder. Inflammation of the external meatus was not uncommon in the boys under 3 years. Vulvitis was present in 57 per cent of the girls and was usually chronic.

Cystoscopy was carried out in 220 cases. Urography was done in 150 cases, and 60 per cent of the urograms showed abnormalities in the upper part of the urinary tract, which, though slight, indicated early changes due to the chronic inflammatory process below.

In all 310 cases the urethra was dilated with metal sounds on one or more occasions (under general anesthesia). Ninety-seven per cent of the patients showed benefit from urethral dilatation. In 42 per cent enuresis continued in spite of repeated treatments but symptoms improved. LANGMANN, New York.

SYNDROMES OF ALKALINE URINE IN INFANCY. HERMANDO MAGLIANO, HECTOR IRON MANARA and TOMAS SLECH, An. Soc. puericult. Buenos Aires **7**:275 (July-Sept.) 1941.

A résumé of the histories is given. The following different clinical pictures were found: (1) gastrointestinal disturbances, dyspepsias and intestinal colics; (2) vulvovaginitis; (3) convulsive states; (4) dystrophies; (5) meningismus; (6) subfebrile temperatures and (7) dermatitis and irritations of the skin. These conditions may be present alone or in mixed types.

Four facts stand out: 1. None of these conditions are cured entirely, and in the majority of patients they are not even much better, with the usual treatments. 2. In all subjects the urine is alkaline. 3. Except in 6 cases the alkalinity was accompanied by phosphaturia.

When by appropriate treatment the reaction of the urine is changed to acid, complete cure is secured.

The authors state these conclusions: 1. The cause of this metabolic disturbance could not be determined. 2. Changing the reaction of the urine to acid entirely cured the patients. 3. There exist some sick infants who are not cured by making the urine acid (phosphaturia). 4. The urine may be alkaline in children completely well. GIFFEN, Toledo, Ohio.

Diseases of the Ductless Glands; Endocrinology

BLOOD AND URINE CHLORIDES IN TWENTY-TWO CASES WITH DIABETES INSIPIDUS. HARRY BLOTNER, Am. J. M. Sc. **202**:222 (Aug.) 1941.

Blotner presents a study of the serum chloride of 22 patients with diabetes insipidus and the total excretion of chloride in the urine of 2 of them.

The serum chloride concentration was found to be normal in these subjects, even though some of them had not taken solution of posterior pituitary for several years. Administration of solution of posterior pituitary did not affect significantly the serum chloride concentration.

The total excretion of chloride in the urine showed some variation from day to day, but the results came within the normal range, even though huge volumes of urine were excreted. Therapy with solution of posterior pituitary did not alter the results appreciably. A considerable restriction of the fluid intake of 1 patient for one day did not change the serum chloride concentration or the salt excretion in the urine.

Patients with diabetes insipidus taking a normal amount of salt maintain a normal serum and urine chloride balance in spite of the exchange of large volumes of fluid. The diuresis of diabetes insipidus does not affect the serum and urine chlorides like the diuretics in normal people, and the antidiuretic action of solution of posterior pituitary does not have an opposite effect on the chloride balance. HENSKE, Omaha.

THE INADEQUATELY TREATED CRETIN. I. P. BRONSTEIN and WILLIAM H. REALS, Arch. Surg. **42**:1049 (June) 1941.

An inadequately treated child with hypothyroidism is discussed. The patient under observation failed to show normal growth and development owing to an erroneous diagnosis of postpertussis encephalitis. When thyroid therapy was

undertaken she improved rapidly. The authors point out that children with deficiency of the thyroid who are not properly treated may present symptoms simulating other conditions which lead to diagnostic errors. In understatured children the basal metabolic rate should be determined if possible. If that is difficult to obtain, studies of ossification of the wrist and knee as well as determinations of cholesterol are valuable. With these aids the diagnosis of hyperthyroidism can usually be established and the proper medication instituted.

KAISER, Rochester, N. Y.

THE DIAGNOSIS OF HYPOTHYROIDISM IN CHILDHOOD. LAWSON WILKINS and WALTER FLEISCHMANN, J. A. M. A. **116**:2459 (May 31) 1941.

The authors review the factors in diagnosis of hypothyroidism from experience with 45 cases in five years and with 50 dwarfs of other types.

Size is always suggestive, particularly the ratio of upper and lower skeletal segments. Retarded osseous development affects the appearance of the nose, delays the eruption of teeth and retards the ossification of the centers of bone formation. These are improperly calcified also.

Mentality is retarded, often irreparably. In hypothyroidism treatment with thyroid produces a prompt response in activity and a slower response in intelligence.

Functional changes are assayed by metabolism tests and by determination of the cholesterol content of the blood and of the excretion of creatine.

The authors present new work on the results of "provocative" treatment with thyroid and thyroxin and the effects of their withdrawals on the metabolism and chemical tests.

HEERSMA, Kalamazoo, Mich.

CREATINE AND CREATININE METABOLISM IN HYPOTHYROIDISM: WITH SPECIAL REFERENCE TO THE LIMITATIONS OF USING CREATININE IN THE URINE AS A STANDARD OF BASAL ENERGY METABOLISM. CH'UAN FAN, J. Pediat. **18**: 57 (Jan.) 1941.

Three cases of hypothyroidism were studied. It was shown that the level of blood cholesterol gave a general indication of the therapeutic effect of thyroid but did not serve as a reliable quantitative indicator of the basal metabolic rate. The degree of creatinuria also did not parallel the level of the basal metabolic rate, either before or after thyroid therapy. On the institution of thyroid therapy, there was a prompt and marked increase of creatinuria. This creatinuria was not due to increased production of creatine but was rather the result of decreased capacity of the body tissues to store or utilize the substance. This is shown by the results of the creatine tolerance tests. It is suggested that such an intolerance might be due to decreased availability of muscle glycogen. The urinary creatinine showed a definite tendency to decrease as the thyroid therapy was continued, especially when the subject was on a meat-free diet. It is shown by simultaneous studies on body weight and nitrogen metabolism that such a decrease could not have been due to loss of active body tissue. It is pointed out that such a decrease must be due to depletion of creatine in the tissue on account of the exaggerated creatinuria during the course of thyroid therapy. This is further supported by the fact that the amount of urinary creatinine temporarily increased when extra creatine was given during the creatine tolerance tests. This decrease in creatinuria following thyroid therapy is contrary to the usual reports but fits in logically with the conception that creatinine is derived from creatine in the body.

RAUL, Cincinnati [AUTHOR'S SUMMARY].

INFANTILISM, OBESITY AND RETINAL DYSTROPHY: A "FORME FRUSTE" OF THE LAURENCE-MOON-BIEDL SYNDROME. RICHARD W. B. ELLIS and FRANK W. LAW, Arch. Dis. Childhood **16**:105 (June) 1941.

A case of the Laurence-Moon-Biedl syndrome is described in which the appearance of the fundi was different from that in typical retinitis pigmentosa.

KELLY, Milwaukee.

Diseases of the Muscles, Bones, Joints and Lymph Glands

NEGATIVE THERAPEUTIC AND METABOLIC EFFECTS OF SYNTHETIC ALPHATOCOPHEROL (VITAMIN E) IN MUSCULAR DYSTROPHY. MEYER M. HARRIS, Am. J. M. Sc. **202**:258 (Aug.) 1941.

Therapeutic effects of synthetic di-alphatocopherol acetate in 5 cases (4 male patients and 1 female) of progressive muscular dystrophy are reported.

Two of the male patients had a familial history of the disease.

The pronounced therapeutic effects of wheat germ oil reported by some investigators were not obtained with the use of synthetic vitamin E.

Some differences in creatine metabolism between experimental nutritional muscular dystrophy in animals and muscular dystrophy in man are pointed out.

The significance of the results are discussed and plans for further investigations are indicated.

HENSKE, Omaha.

THE THERAPY OF LYMPHOGRANULOMA VENEREUM. R. BRANDT, South. M. J. **34**:941 (Sept.) 1941.

The author states that the acute bubo of lymphogranuloma venereum is profoundly influenced by chemotherapy with sulfanilamide and its derivatives and compounds. Late manifestations do not occur after intensive early treatment, but chronic lesions, especially rectal strictures often develop without preceding acute manifestations.

Ulcerative and hyperplastic lesions are less favorably influenced. Those of short duration usually yield to prolonged chemotherapy, possibly reenforced by vaccinotherapy or physical therapy. Chronic ulceration and elephantiasis are, however, resistant to therapy.

In rectal stricture, pain, rectal leukorrhea and general complaints respond, and often completely yield, to chemotherapy. Stenosis is influenced by mechanical dilatation.

Patients seen in the acute stage of lymphogranuloma venereum may expect complete healing. The treatment of neglected lesions or those developing without a preceding acute state is less promising.

SCHLUTZ, Chicago.

CONGENITAL, DEVELOPMENTAL AND ACQUIRED CHARACTERISTICS OF THE SPINE AND THEIR RELATION TO INJURY. MERRITT L. JONES, Wisconsin M. J. **40**:574 (July) 1941.

Changes in the spine incident to age, to anomalies of structure and to the stress and strain of life are many and often confusing. Jones reviews them in detail, as they are likely causes of errors in diagnosis. The danger of calling these disturbances traumatic is pointed out.

JANNEY, Wauwatosa, Wis.

CONTROL OF RHEUMATISM. Editorial, Brit. J. Phys. Med. **4**:49 (April) 1941.

Attention is drawn to a recent booklet by Lord Horder on "Rheumatism—A Plan for National Action." This booklet was prepared in collaboration with the Empire Rheumatism Council. The editor comments on the important place given by Lord Horder to the various forms of physical therapy in the treatment of rheumatism. He includes in his general plan of treatment artificial fever therapy, massage, physical exercises, manipulative treatment and hydrotherapy.

HARTMAN, Cleveland.

SOME STUDIES ON LYMPHANGIOMAS. GUSTAVO CARDELLE and ARGELIO G. LOPEZ, Arch. de med. inf. **10**:104 (April-June) 1941.

A rather full résumé of the subject is given, and 3 illustrative cases are reviewed. The authors believe surgical removal to be the treatment of choice. One child was treated by punctures with 60 per cent sodium citrate with no result.

SANFORD, Chicago.

A Case of Albers-Schönberg Disease. J. P. Magalhães and A. R. Filho, Rev. méd. munic. **11**:58 (July) 1941.

A 9 year old girl was found on routine examination to have Albers-Schönberg disease. Roentgenograms of her bones are shown. There is an excellent review of the literature, from which the authors have collected 126 cases. They regard Leriche and Policard's conception, that the sclerotic epiphysial layers of the bones of the hands and feet are wider near the ossification nuclei, as the most probable etiologic factor.

Sanford, Chicago.

Effect of Prostigmin and Disturbance of Carbohydrate Metabolism in a Severe Case of Myasthenia Gravis. Rolf Kostmann, Acta med. Scandinav. **108**:351, 1941.

The subject was a 26 year old woman who had suffered from the disease for six years. Although at first injections of prostigmine of methylsulfate were beneficial, after a few months both the dose and the frequency of injections had to be increased. If an arm was made ischemic by compression with a blood pressure cuff for ten minutes while the drug was injected, this arm after release of circulation showed very little increase in power, whereas if the arm was compressed five minutes after an injection, this arm showed the same improvement as its mate. This suggests that the drug in active form disappears from the circulation within ten minutes but that its local action on the muscles lasts for several hours.

Although the author previously reported cases in which small doses of epinephrine enhanced the beneficial action of prostigmine, subcutaneous injection of 1 mg. of epinephrine hydrochloride in this patient resulted in aggravation of the symptoms. The rise in blood sugar following the injection of this dose of epinephrine was insignificant unless prostigmine was injected shortly before. Injection of epinhprine was always followed by a rise in the systolic blood pressure. Intravenous injection of 100 cc. of 25 per cent dextrose was followed by improvement in muscle power within ten minutes, as shown by dynamometric readings.

Kajdi, Baltimore.

Skin Diseases; Allergy

Lupus Vulgaris. Robert Aitken, Brit. J. Phys. Med. **4**:66 (May-June) 1941.

The incidence of this disease in the dermatologic department of the Royal Infirmary of Edinburgh has varied from 0.5 to 1.0 per cent in the last ten years. Fifteen to twenty years ago the percentage varied from 2.8 to 4.0. In an analysis of 294 cases, it was found that in almost 25 per cent the lupus occurred in the age period of 6 to 10 years, and more than half of it began during the school life of the child. It affected the face in 77 per cent of the cases.

A diet rich in vitamins and the careful use of caustics, of tuberculin and of general ultraviolet irradiation are recommended. Treatment with roentgen rays is condemned.

Local treatment with a Finsen-Lomholt lamp is found most satisfactory. This is a carbon arc lamp with a complex lens septum.

The author presents 2 case studies.

Hartman, Cleveland.

A Simple and Effective Therapy of Ichthyosis. C. E. Ljungström, Acta med. Scandinav. **108**:98, 1941.

Based on the observation of a case of severe ichthyosis, in which only those areas of skin where the patient complained of excessive perspiration were free of lesions, the author applied a hydrous wool fat ointment containing 10 per cent sodium chloride daily after a 3 per cent sodium chloride solution bath. He was able to keep the patient symptomless for five months.

Kajdi, Baltimore.

Society Transactions

SOCIETY FOR PEDIATRIC RESEARCH

GEORGE M. GUEST, M.D., *President*

MITCHELL I. RUBIN, M.D., *Secretary*

Annual Meeting, Skytop Lodge, Skytop, Pa., April 29-30, 1942

Afternoon Session

Wednesday, April 29

Organic Phosphates of the Blood and Mineral Metabolism in Diabetic Acidosis: President's Address. DR. GEORGE M. GUEST, Cincinnati.

This paper was published in full in the September issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN, page 401.

Refractory Rickets: Mechanism of Therapeutic Action of Calciferol. DR. B. R. ROBERTSON, New York; DR. R. C. HARRIS, Rochester, N. Y., and DR. D. J. MCCUNE, New York.

In 1940 Harrison and Harrison presented to this society evidence that one effect of vitamin D in the healing of canine rickets is to accelerate the rate at which the renal tubular epithelium resorbs phosphate from the glomerular filtrate. The occasion to treat a child suffering from refractory rickets has provided the opportunity to verify this phenomenon in human beings and to gain some insight into the pathogenesis of this species of rickets.

The patient, a 10 year old Mexican boy, had active rickets of extreme severity. That the disease was of the refractory variety was shown by the results of chemical studies of the blood and roentgen examinations, which excluded the participation of those peculiarities of metabolism found in classic renal rickets, the Fanconi syndrome and the types described by Albright and his associates, Boyd and others.

Treatment was carried out with large doses of vitamin D. During the first three weeks the boy received an average of 200,000 U. S. P. units daily. The intake of minerals was kept fairly constant. The initial concentration of inorganic phosphorus in the serum was 2.6 mg. per hundred cubic centimeters. At this time the renal clearance of phosphate was 8.8 cc. per minute. Thirteen days after treatment was started the serum phosphorus reached 3.6 mg., incipient healing was evident in roentgenograms and the renal clearance of phosphate had fallen to 5.6 cc. per minute. Rapidly progressive mineralization of the rachitic metaphyses was accompanied by an increase of serum inorganic phosphorus to 5.1 mg. per hundred cubic centimeters and a decline of phosphate clearance to 3.3 cc. per minute. Simultaneous determinations of the rates of glomerular filtration and of phosphorus clearance before treatment and when healing was advanced show that these changes were brought about by increased efficiency of the tubular epithelium in reabsorbing phosphorus from the filtrate. Harrison's "equilibrium concentration" —that is, the renal threshold—rose from 2.3 to 4.9 mg. per hundred cubic centimeters.

Improved intestinal absorption of phosphorus accompanies the successful treatment of refractory rickets. This has been shown in balance studies carried out

according to classic procedures. Since the urinary phosphorus is apt to remain unchanged rather than to decrease during treatment, the role of improved renal efficiency in restoring a physiologic concentration of phosphorus within the body has escaped general recognition.

Our observations emphasize the fundamental similarity between refractory rickets in children and experimental rickets in animals. They further emphasize the importance of the renal component in refractory rickets. The disease may be conceived to depend on a functional defect of an enzyme system of which vitamin D forms the prosthetic group and which is responsible for the absorption of phosphate from the intestine and its reabsorption from the glomerular filtrate. It appears possible to produce an adequate amount of the enzyme through the mass effect of large amounts of vitamin.

The Calcium and Phosphorus Requirements of Premature Infants. HELEN R. BENJAMIN, PH.D.; DR. HARRY H. GORDON and ELEANOR MARPLES, B.A., New York.

This article will be published in full in a later issue of AMERICAN JOURNAL OF DISEASES OF CHILDREN.

Blood and Tissue Phosphatase in Experimental Scurvy. DR. HARRY SHWACHMAN and BERNARD S. GOULD, PH.D., Boston.

A study of 28 cases of infantile scurvy revealed that the alkaline phosphatase in the serum is greatly reduced in the acute stage of the disease and that the administration of ascorbic acid brings about a rise within a period of ten days.

In order to ascertain the significance of these changes, observations were made on a group of approximately 175 guinea pigs. These observations, together with the histologic picture in scurvy, suggest that the osteoblasts are the source of the serum enzyme. Guinea pigs fed a scorbutogenic diet show a steady decline in the alkaline serum phosphatase, often reaching extremely low levels. There is likewise a decrease in the concentration of alkaline phosphatase in the skeletal tissue, whereas no change in concentration occurs in the other organs studied (intestinal mucosa, kidneys, adrenal glands, liver and spleen).

The administration of ascorbic acid to scorbutic animals even in fractional curative dosage results in a rapid rise in the serum alkaline phosphatase, and the subsequent withdrawal of ascorbic acid will again bring about a lowering of the enzyme. These changes in the serum reflect the change in concentration of phosphatase in the skeletal tissues.

The administration of ascorbic acid to healthy guinea pigs does not alter the phosphatase concentration of the serum or of skeletal tissue, nor does ascorbic acid activate the low serum phosphatase of scorbutic guinea pigs in vitro.

There is no apparent change in the concentration of "acid" phosphatase in the serum or tissues or in the serum inorganic phosphate of scorbutic animals.

Acute Ketosis in Glycogen Disease. DR. RICHARD G. HODGES, New York.

Seven hour chemical observations in six crises of ketosis occurring in 4 patients with glycogen disease were presented. The carbon dioxide–combining power and the blood sugar content were low and the nonprotein nitrogen and total serum lipids high; acetone was present in excess in the urine or serum.

The newer concepts of fat metabolism have been reviewed recently by Stadie. Briefly, they are as follows: When the body is deprived of dextrose as a source of fuel, it falls back on fat for its caloric needs. Fifty to 60 per cent of the calories supplied by fat is due to a direct oxidation of the fatty acids in the tissues. The remainder is supplied by a mobilization of fat into the blood and thence to

the liver, where it is broken down into ketone bodies. These ketone bodies are then burned in the tissues. The process is relatively inefficient and contains two principal bottle-necks. First, the depots may mobilize more fat than the liver is able to break down. The result is hyperlipemia. Secondly, the tissues are able to utilize ketone bodies at only a fixed and relatively slow rate. If the output of ketones by the liver exceeds this rate, the result is ketosis. Stadie has applied this mechanism to diabetic ketosis. It is the purpose of this presentation to indicate that the same mechanism can be applied to glycogen disease.

In glycogen disease the body is unable to mobilize dextrose from the liver and must therefore fall back on direct absorption from the intestine as the source of circulating sugar. If the dietary supply fails, it is to be expected that the mechanisms that have been described will be put in motion. Each of the crises was immediately preceded by an episode that restricted the dietary intake. Not all the patients responded in exactly the same way. Three of the patients had hyperlipemia and ketosis, but the fourth had only the latter.

Three of the crises were fatal. The other three responded to repeated injections of dextrose solution and to parenteral administration of fluids designed to combat the acidosis and dehydration. There is some evidence that lactate solutions are contraindicated.

In 1 patient an attempt was made to stabilize the variations in blood sugar by dietary means. This was done on the basis of Dr. Howard Masons' interpretations of the absorption curves of monosaccharides. When levulose or galactose was given, it was rapidly removed from the blood, whereas dextrose circulated for an abnormally long time. The patient was therefore changed to a Mull-Soy formula so that the diet would supply dextrose rather than galactose. (Mull-Soy is a proprietary mixture of soybean flour, soybean oil, dextrose, sucrose, calcium phosphate and carbonate, salt, soybean lecithin and water.) Dextrose solution was given between feedings. This resulted in a fall of total serum lipids and a gain in weight. However, even after recovery, when the serum and urine were qualitatively negative for ketones, quantitative determination of the serum ketones gave a fasting value of 4.2 mg. per hundred cubic centimeters while the blood sugar content was 29 and 2.7 mg. per hundred cubic centimeters one and a half hours after feeding, when the blood sugar content was 97. The normal range for serum ketones is 0.1 to 1 mg. per hundred cubic centimeters.

A Quantitative Description of Changes in Plasma and Interstitial Fluid Volumes Occurring in (1) Dogs with Operative Fistulas of the Accessory Pancreatic Duct and (2) an Adrenalectomized Dog After Withdrawal of Replacement Therapy. DR. VICTOR RUDOMANSKI, Brooklyn.

In 1928, Gamble and McIver, studying the chemical changes in extracellular fluid during the course of dehydration through loss of the external secretions of the pancreas in dogs, were impressed by the stability of the plasma volume in spite of the pronounced loss of weight. They concluded that in slowly progressing withdrawals of the extracellular fluid the successful operation of the mechanisms concerned in stabilizing plasma volume is readily discernible.

Because of the importance of this physiologic concept to clinical medicine, it was deemed worth while to review the experiment in the laboratory for the purpose of describing the essential data in reasonably quantitative terms. To this end, longitudinal studies of the volume of plasma and of interstitial fluid were made on 2 dogs in which fistulas of the accessory pancreatic ducts were successfully created.

Plasma volume and interstitial fluid volume were determined simultaneously by a method developed by Gregersen and Stewart, with the exception that the concentration in the plasma of the blue dye, T 1824, employed for the measurement of volume was determined by the photoelectric microcolorimeter. For the deter-

mination of the plasma thiocyanate concentration in the measurement of interstitial fluid volume, the Dubos microcolorimeter was used.

In addition, for purposes of contrast, analogous data obtained from an adrenalectomized dog after withdrawal of replacement therapy was presented.

Effect of Alterations in Electrolyte Exchange in Bronchial Asthma of Children. Dr. Marguerite Booth and Dr. A. V. Stoesser, Minneapolis.

Previous investigations by one of us (A. V. S.) have revealed that children with intractable asthma experience clinical relief from artificial hyperpyrexia, ingestion of potassium chloride and administration of pitressin when maintained on a diet low in sodium chloride. It was assumed that a depletion of the body sodium was the basis for the improvement, but no determinations of the mineral output were made. Further studies have been conducted on 6 children with chronic asthma. They were placed in the pediatric metabolism ward and subjected to various forms of therapy. During most of these periods, they were given a diet extremely low in salt, consisting of a formula having adequate caloric and dietary constituents with vitamin supplements. At all times the diet and fluid intake were measured, and the output of urine and stool was analyzed for the electrolytes.

The first 4 subjects, a boy of 12 and 3 girls of 10, 12 and 13 years, received a daily dietary intake of 120 mg. of sodium, 330 mg. of potassium and 180 mg. of chlorine. Artificial fever therapy was given on five occasions, the temperature of each patient rising to 40 C. (104 F.) and remaining at this level for at least five hours. There were four periods of ingestion of potassium chloride, ranging from four to eight days. The amount of the salt given each day varied from 2 to 12 Gm. Pitressin was administered at intervals hypodermically for twenty-four to thirty-six hours on two occasions. The dose ranged from 0.2 to 0.5 cc. every three hours. All of these procedures decreased the asthmatic symptoms.

The remaining 2 patients were girls, 16 and 17 years old, receiving 174 mg. of sodium, 477 mg. of potassium and 264 mg. of chlorine. There was one period of therapy with potassium chloride and five with pitressin, with good results.

The boy and 2 of the girls, 10 and 17 years of age, were subjected to three periods of ingestion of sodium chloride, ranging from six to eight days. The daily dose of the salt varied from 1 to 30 Gm. The 17 year old girl received subcutaneously adrenal cortex extract and the single adrenal cortical factor represented by desoxycorticosterone acetate, each for five day periods, the former in doses of 8 cc. daily and the latter 8 to 20 mg. daily. There was severe aggravation of the asthma. The adrenal cortex extract was administered also to the 16 year old girl, but she became ill and the use of the preparation had to be discontinued.

The analytic data revealed that there was a pronounced loss of electrolytes through the skin during hyperpyrexia, reducing the urinary excretion to a minimum. The ingestion of potassium chloride caused large quantities of potassium and chlorine to be excreted. Sodium was also washed out with these ions until it became extremely low. During pitressin therapy sodium, potassium and chlorine were retained, but after the use of the hormone was discontinued, there was an excretion of large amounts of these elements, particularly of sodium and chlorine. When sodium chloride was added to the patients' diets in considerable quantities, the diuresis which followed swept out a significant amount of potassium. Adrenal cortex extract produced a retention of sodium but permitted the excretion of potassium. This effect was accentuated by the administration of desoxycorticosterone acetate.

Therefore, it is apparent that any form of therapy which favors the loss of sodium from the body gives some relief from asthmatic symptoms, while the retention of this electrolyte leads to more severe asthma.

The Antagonism of Adrenal Cortical Extract and Pitressin in Human Diabetes Insipidus. Dr. John A. Anderson, Minneapolis.

The antagonism of adrenal cortical extract and pitressin in their effect on the excretion of water and electrolytes was studied in a 9 year old boy with diabetes insipidus. While the subject was maintained on a low mineral diet, the effect of adrenal cortical extract was observed during a water-restricted period and a period of free fluid intake. The effect of pitressin and pitressin plus adrenal cortical extract on the excretion of water and electrolytes was observed during a period of free fluid intake.

The administration of adrenal cortical extract was without effect on the excretion of sodium and chlorine during a water-restricted period. When an adequate fluid intake was permitted, adrenal cortical extract characteristically reduced the excretion of sodium and chloride. There was, however, a reduction in the potassium excretion. When pitressin was given during free ingestion of fluid, the excretion of sodium and chloride increased and the excretion of potassium decreased. When adrenal cortical extract was given during pitressin antidiuresis, the excretion of sodium and chloride was reduced and the excretion of potassium increased. These observations on the excretion of potassium suggest that adrenal cortical extract is unable to produce its usual effect in increasing the excretion of potassium unless the facultative reabsorption of water induced by pitressin is present. The water exchange was increased by the administration of adrenal cortical extract, either with or without pitressin antidiuresis.

These observations on a human subject support the previously observed concept of a physiologic antagonism between the hormones of the adrenal cortex and the antidiuretic substance of the posterior lobe of the pituitary gland.

Available Carbohydrate Reserves of Premature Infants. Dr. David H. Weintraub and Dr. Edward M. Bridge, Baltimore.

The present study is an effort to clarify the caloric requirements of premature infants by utilizing the rate of fall of the respiratory quotient during fasting as an approximate measure of available carbohydrate reserves. High reserves are indicated by a slow fall in the respiratory quotient over nine hours of fasting from a level of 0.92 to 0.95 to a minimum of 0.83 to 0.85. A rapid fall to 0.70 to 0.75 in less than nine hours, occasionally in six, indicated low reserves of available carbohydrate. A previous report to this society showed that in rabbits high respiratory quotients are associated with high values for liver glycogen and low respiratory quotients with low values for glycogen; at a quotient of 0.80 or below, liver glycogen is at a minimum. This confirms the impression that a respiratory quotient below 0.80 indicates low available carbohydrate reserves in premature infants.

The average respiratory quotient between feedings is 0.89, and after six hours of fasting it is 0.83 for premature infants above birth weight, over 3 weeks of age and gaining weight. The period of early loss of weight is accompanied by low respiratory quotients between feedings; as adequate food is ingested and the weight increases, the quotient gradually rises to normal levels but later may drop with inadequate food. The lack of satisfactory gain of weight during the initial two or three weeks of life, at a time when the carbohydrate reserves may be abnormally high, suggests that the failure to gain is not due to inadequate food. In 1 case, the respiratory quotient rose to 1.03, suggesting conversion of carbohydrate into fat as a means of disposal. As weight is gained more rapidly, the carbohydrate reserves gradually return to normal levels.

From the data observed, it is believed that 75 to 90 calories per kilogram daily is adequate during the initial two or three weeks of life and thereafter 100 to 125 calories per kilogram will suffice.

The Experimental Production of Achylia Pancreatica. DR. SIDNEY FARBER, Boston.

Previous studies have shown that a lesion of the pancreas characterized by dilatation of ducts and acini, inspissation of secretion and variable degrees of atrophy of the parenchyma and fibrosis is found in constant association with two apparently distinct clinical pictures in early life: (1) meconium ileus in the newborn infant, and (2) that variant of the celiac syndrome known as "cystic fibrosis" or "pancreatic fibrosis." The fundamental disturbance brought about by this lesion is pancreatic achylia, as indicated by the histologic picture and demonstrated in the pancreatic variant of the celiac syndrome by enzyme analysis. The explanation for such divergent clinical pictures caused by the same lesion is found in the time of occurrence of the pancreatic achylia; if the achylia is present during the latter part of intrauterine life, a physically altered meconium will result and will cause intestinal obstruction shortly after birth; if the achylia is not present until after the neonatal period, the disease picture will be that of the celiac syndrome.

Enzyme studies carried out in collaboration with Dr. Charlotte Maddock and with Dr. Harry Shwachman have suggested a tentative division of the celiac syndrome into three main groups: (1) true celiac disease, with normal enzyme values; (2) selective enzyme deficiencies, with important diminution in the amount of any one of the three pancreatic enzymes in the duodenal juice when the other two are within normal limits, and (3) "cystic" or "pancreatic fibrosis," with almost complete absence of lipase, amylase and trypsin—i. e., pancreatic achylia. This is the only member of the celiac group proved so far to stand in causal relationship to an organic lesion of the pancreas. Achylia is produced probably by an intrapancreatic disturbance to the formation, liberation or passage into the duodenum of pancreatic enzymes.

From postmortem studies my colleagues and I have been able to conclude: (1) that congenital atresia or stenosis of the pancreatic ducts is a rare cause of pancreatic achylia; (2) that neither a deficiency of vitamin A nor an infection with a filtrable virus is of primary importance in the production of the pancreatic lesion or essential in any way to its occurrence, although either or both may complicate the disease picture once the lesion has been produced, and (3) that the widespread occurrence in the upper respiratory and intestinal tracts, the gallbladder and other places of dilated glandular structures filled with inspissated material, giving a picture similar to that found in more distinctive form in the pancreas, indicates that in most instances this pancreatic disorder is a part of a generalized disease, with greatest involvement, however, of the pancreas.

The demonstration that the clinical picture of the celiac syndrome associated with proved pancreatic achylia may occur at a time when the lesion of the pancreas is confined to inspissated materials in the acini and small ducts without any evidence of "cystic fibrosis" or atrophy of the organ and the viscid character of the scanty pancreatic juice in these patients as compared with the thin watery secretion of normal patients or those with true celiac disease gave support to the suggestion of Wolbach that the pathogenesis of this pancreatic lesion resides in the production of an abnormal secretion and indicated the direction for an experimental approach to this problem. Accordingly, a series of kittens was treated over a period of two to eight weeks by injections of parasympathetico-mimetic drugs. The best results were obtained when pilocarpine hydrochloride was administered subcutaneously three times a day in doses which were increased from 0.5 mg. at the onset of the experiment to 10 mg. as tolerance to the drug increased. Extreme loss of weight and severe nutritional disturbance were the chief clinical features observed. Histologic examination of the pancreas revealed a lesion similar in all important respects to that found in infants suffering from pancreatic achylia. The acini and small ducts were filled with thick, homogeneous, eosinophilic material. That dehydration or starvation was not of primary importance in the production of this lesion was demonstrated in control experiments.

These studies are being continued to determine the nature of the disturbance to the secretory mechanism in the pancreatic acini, which appears to be of fundamental importance in the pathogenesis of the lesion responsible for pancreatic achylia.

The Roentgenologic Pattern of the Small Intestine in Infants and Small Children. Dr. Henry Zwerling, New York, and Dr. Waldo E. Nelson, Cincinnati.

Changes have been described in the roentgenologic pattern of the small intestine, especially of adults, which have been considered to be characteristic of certain deficiency states, as, for example, celiac disease, sprue, nontropical sprue, vitamin B deficiency, hypoproteinemia, acholia and allergy. Doubt that such patterns are necessarily indicative of abnormalities in children was raised when presumptive diagnoses of the celiac syndrome were made on the basis of roentgenologic studies of the small intestine for several children who had no clinical manifestations of the disease.

In view of these observations it appeared necessary to study the roentgenologic patterns of the small intestine in presumably healthy infants and children in order to establish, if possible, a base line. To the time of writing, 77 infants and children, ranging in age from 3 months to 11 years, have been studied. Of these, 20 were from the well baby clinic, 45 from an orphanage and 12 from better than average homes. The orphanage children received supplementary vitamins in the form of percomorph liver oil and a proprietary mixture of vitamins.

In the roentgenologic pattern of the healthy adult, the barium sulfate is observed in a continuous stream and there is a regularity of the mucosal markings. There are no pronounced variations in the caliber of the lumen except for areas of narrowing where peristalsis is active. Flocculation is of the powdery, even type, and the meal enters the distal portion of the ileum or cecum in one and a half to six hours.

In the deficiency states there are coarsening or obliteration of the mucosal markings, segmentation, irregular flocculation and, in some instances, dilatation. The pattern in gastrointestinal allergy is that of hypertonicity, or narrowing, of the lumen. This is especially marked in the lower one third of the small intestine. The films in the first part of the series, as for example at one-half hour and one hour, may reveal a normal pattern, whereas the later films show abnormalities.

In our series of apparently healthy children all of these signs except dilatation have been encountered in the majority of instances. So-called normal adult patterns were distinctly rare and occurred in 5 children. The earliest age at which such a pattern was observed was 11 months. So-called "infantile," or "deficiency," patterns were observed in 38 infants and children. The remainder had patterns which could be interpreted as being transitional between the adult and infantile types. Thus, if the present criteria for the "normal" small intestine were employed in the interpretation of the roentgenograms in this series of children, the majority of them would be considered as suffering from some deficiency state. While more complete correlation studies are required, it scarcely would appear justifiable on the basis of such evidence to consider them as abnormal. Among other factors, the possibility of emotional disturbance has been considered as a cause of the observed roentgenologic patterns. While we do not have sufficient studies to supply an answer to this question, we do have repeated studies on 5 children. In 3 of these there was distinctly less manifestation of emotional upset at the time of the second examination. The intestinal pattern of these children was essentially the same at each examination.

On the basis of this preliminary study, it would appear doubtful that the roentgenologic criteria employed in the evaluation of the small intestine of adults can be applied at the present time in the study of infants and children.

Evening Session

Wednesday, April 29

Symposium on Nutritional Research as Related to Children in Wartime

Strategic Nutrients. Guest Speaker: DR. JOHN R. MURLIN, Professor of Physiology, University of Rochester and Chairman Committee on Research, Food and Nutrition Board of the National Research Council.

Observations on Growth Progress as Indication of Faulty Nutrition. DR. HAROLD C. STUART, Boston.

The Effect of the War Upon the Distribution of Available Nutrients. DR. JOSEPH STOKES JR., Philadelphia.

Open Discussion.

Morning Session

Thursday, April 30

Qualitative Differences in the Streptococcus Antifibrinolysin Test. DR. PAUL L. BOISVERT, New Haven, Conn.

Milstone has recently demonstrated that the plasma clots of rabbits are resistant to lysis by human strains of hemolytic streptococci because they lack a substance —"lytic factor"—which is present in normal human serum. The addition of "lytic factor" to rabbit plasma results in rapid liquefaction of the clot by fibrinolysin. This observation was of considerable interest to my colleagues and me because of its possible clinical application, since it might explain some of the apparently nonspecific positive results of streptococcus antifibrinolysin tests (resistant clots) which we have observed in infants and in children.

Blood of newborn infants frequently gives a positive reaction in spite of the fact that there is no clinical or bacteriologic evidence of a recent hemolytic streptococcic infection in the mother and her test is negative.

As a starting point for the present study such blood of newborn infants was compared with that of children who were convalescing from scarlet fever and other hemolytic streptococcic infections. All had maxillary positive reactions to streptococcus antifibrinolysin tests. The results indicate that the resistant clots of the newborn depend on a different mechanism than those observed in patients recovering from a hemolytic streptococcic infection. In newborn infants resistance is apparently due to the absence of a substance, since their clots are rapidly dissolved when normal serum has been added and resistance cannot be passively transferred to normal plasma by the addition of their serum. The reverse is true of the blood of patients recovering from a hemolytic streptococcic infection; that is, the resistance is due to the presence of a substance which is transferable.

Current studies indicate that the positive reactions to antifibrinolysin tests (resistant plasma clots) encountered in patients with severe nonstreptococcic diseases are in many cases due to absence of a substance—presumably "lytic factor" of Milstone—and not to the presence of streptococcus antifibrinolysin. In other instances both absence of a lytic factor and presence of antifibrinolysin have been demonstrated.

True and False Tests for Streptococcus Antifibrinolysin in Newborn Infants. Dr. J. A. Lichty Jr. and Dr. G. K. Anderson, Rochester, N. Y.

This paper will be published in full in a later issue of the American Journal of Diseases of Children.

Sulfanilamide as a Prophylactic Agent in Rheumatic Fever. Dr. Caroline A. Chandler, Baltimore.

This investigation was undertaken to test the value of small doses of sulfanilamide in the prevention of recurrences of rheumatic fever and to conduct concurrent bacteriologic studies which might throw some light on the possible role of the beta hemolytic streptococcus in recurrences of rheumatic fever.

During the first year of the study, 18 patients were given sulfanilamide. For 1 patient administration of the drug was stopped because of a toxic reaction and for 1 because of questionable recurrence of rheumatic fever. The remaining 16 patients who were given sulfanilamide throughout the year showed no evidence of rheumatic activity. Of the 17 patients in the corresponding control group, 5 had recurrences of rheumatic fever; in 2 the attacks were severe and in 3 they were mild.

Streptococci of varying virulence were isolated from 5 patients in the group treated with sulfanilamide. Three were group A and two were group C strains. None of the patients from whom these were isolated gave any clinical evidence of streptococcic infection, and in none did rheumatic recurrences develop.

In the control group streptococci were isolated from 4 patients. All four strains belonged in group A. One highly virulent organism was associated with a severe streptococcic infection, and this patient subsequently suffered a severe recurrence of rheumatic fever. One relatively avirulent strain not associated with a streptococcic infection was isolated from a patient who had a mild attack of chorea. Two of the strains isolated, however, were associated with neither streptococcic nor rheumatic episodes. Moreover, recurrences of rheumatic fever were observed in 3 patients from whom no streptococci were cultured.

In the 1941-1942 period, the results to the date of reporting were as follows: The administration of sulfanilamide was started for a total of 29 patients. The use of the drug was discontinued in three instances because of toxic reactions and in one instance because the patient was uncooperative. The remaining 25 patients who were kept on the drug showed no evidence of rheumatic activity, nor were streptococci isolated from any patients in this group. In the corresponding control group of 24 patients, there were no rheumatic exacerbations throughout the year. Streptococci, however, were isolated from 3 patients in the control group, and one of the strains isolated fell into the virulent category.

These data are insufficient to allow any definite conclusions to be drawn on either the occurrence or the virulence of hemolytic streptococci relative to rheumatic exacerbation. These observations, though few, are in line with those reported by Kuttner on a larger series of cases.

With regard to the value of sulfanilamide as a prophylactic agent in rheumatic fever, even though there have been no recurrences this past winter in either treated or control groups, out of a total of 42 patient-seasons over the two year period, only 1 patient treated with sulfanilamide manifested a questionable recurrence of rheumatic fever (and this within two weeks after beginning drug therapy). Among the control subjects in the corresponding period of time, of a total of 41 patient-seasons, there were 5, or over 10 per cent, recurrences of rheumatic fever, and two of the attacks extended into the second year.

Subcutaneous Administration of Sodium Sulfadiazine in Physiologic Solution of Sodium Chloride. Dr. David M. Greeley and Dr. Gilbert M. Jorgensen, New York.

Investigations are in progress to determine the practicability and safety of subcutaneous administration of sodium sulfadiazine to infants. At the present time

more than forty hypodermoclyses of 0.5 per cent sodium sulfadiazine in physiologic solution of sodium chloride have been given in amounts sufficient for therapeutic requirements. No local or general reactions have been observed. Determinations of the sulfadiazine in the blood have demonstrated that adequate concentrations in the blood may be obtained within one hour after the hypodermoclysis is given and that administration of sodium sulfadiazine by the subcutaneous route once in twelve hours is often enough to maintain an adequate and reasonably constant blood concentration.

The Rh Factor in Erythroblastosis. DR. EDITH L. POTTER, Chicago.

The Rh factor discovered by Landsteiner in 1940 is an antigenic substance normally found in the blood of 85 per cent of all human beings. It is present only in the blood cells; immune bodies against it do not exist, but isoagglutinins can be produced by the introduction of Rh-positive cells into the blood stream of a person with Rh-negative blood. Levine, Stetson, Burnham and Vogel found only 7 per cent of 253 women who were stated to have given birth to infants suffering from erythroblastosis to have Rh-positive blood. Levine and his co-workers postulated that a fetus inheriting the Rh factor from the father may cause immunization of a mother who does not have the Rh factor by the escape into her circulation of cells from the fetal vessels in the placenta. Immune bodies thus produced may pass back through the placenta in a subsequent pregnancy and may affect the fetal hemopoietic system adversely, thus causing the condition known as erythroblastosis.

During the past several years I have examined histologically the tissues of over 3,000 fetuses and infants dying in the first few days of life. For approximately 120 a diagnosis of erythroblastosis was made at some time by some one connected with the case. For about one third the diagnosis was not confirmed by autopsy, and, although anasarca, jaundice or some increase in nucleated red blood cells may have been present, histologic evidence of erythroblastosis could not be found.

Blood has been obtained from 81 of the mothers. Of 50 for whose infants the diagnosis of erythroblastosis was established at autopsy; 86 per cent have blood Rh-negative to three testing serums and 14 per cent have Rh-positive blood; of 31 for whose infant the final diagnosis was other than erythroblastosis only 15.5 per cent have blood Rh-negative to three testing serums, 12.5 per cent have blood Rh-positive to at least one out of three testing serums and 72 per cent have blood Rh-positive to all.

In order to establish the incidence of the Rh factor in women with unsuccessful pregnancies from causes other than erythroblastosis, blood was obtained from 45 who had had spontaneous abortions and 36 whose infants died or were born dead from various causes. In both groups the blood of 75 per cent was Rh-positive, of 11 per cent Rh-negative to three serums and of 14 per cent Rh-negative to at least one of three serums. The incidence in all groups in which infant death was not due to erythroblastosis approximates that found in the general population.

Anti-Rh agglutinins have been demonstrable in the blood of only 8 of these mothers; the infants of 7 of these died of erythroblastosis and in the child of 1 there was no evidence of this disease.

Two infants with erythroblastosis have been found with Rh-negative blood; 1 husband had Rh-negative blood.

These hematologic studies confirm Levine's findings of a high incidence of Rh-negative blood in women who give birth to infants with erythroblastosis. The diagnosis of erythroblastosis, especially for infants who survive, is extremely difficult to establish with certainty. It is possible in instances in which the hematologic findings are not in accordance with this theory that the infant is actually suffering from some other disease.

Adaptation of a Microphotometric Method of Measuring Skeletal Mineralization to a Longitudinal Growth Study. P. B. MACK, PH.D., Philadelphia.

The photographic recording microphotometer described by Mack, O'Brien, Smith and Bauman and by Mack and Smith has been used to evaluate skeletal mineral density in a longitudinal study conducted at the Children's Hospital of Philadelphia since 1934. The use of a microphotometer in making a photographic tracing through a certain path in the roentgenogram of a human bone was begun by me in 1937, after ten years of previous study using the same general technic with roentgenograms of experimental animals.

The photographic tracing method using the photoelectric microphotometer has been found to be highly objective and to afford an excellent criterion for measuring degree of mineralization of bones, as judged by the following evidence: (1) A coefficient of correlation of 0.83 ± 0.003 has been found between bone ash and mineral density of experimental animals when this technic is used to measure mineral density. (2) Calibrations of the technic, with a large number of voltages for exposure and different times of development used on roentgenograms of human beings and of experimental animals, on the same subject in each instance, have shown that the same mineral index values are obtained when the bone tracing is corrected according to the deviation of the heights of the steps of a standard ivory or metallic phantom, or ladder, placed on each film as a fixed object of reference. (3) According to a preliminary study with bones of a human cadaver, a high correlation between bone ash and mineral index is indicated. (4) Changes in the skeletal mineral index as found by this experimental procedure, both of experimental animals and of human subjects, have been found to follow closely certain changes in the dietary.

Treatment of Leukemia in Children with Radioactive Phosphorus. DR. LOUIS K. DIAMOND and DR. SHIELDS WARREN, Boston.

Leukemia in children is usually of the acute type. Roentgen therapy is therefore of limited value. In previous papers from San Francisco and Boston it had been shown that radioactive phosphorus produced in the cyclatron causes biologic changes similar to those following irradiation by roentgen rays or radium. Leukemia has been treated by various observers with radioactive phosphorus, but in these cases the disease has been chiefly the chronic form seen in adults.

In the last fourteen months we have administered radioactive phosphorus to 12 children with leukemia, chiefly of the acute form. The material was given intravenously in measured amounts.

In all, forty-six injections were given to 12 patients, and at one time only was there an immediate reaction, due to deterioration of the diluent. The cases were divided into three groups according to the clinical changes seen in each.

In the first group of 5 patients no clinical improvement was evident. In these the disease was in the most acute form. Though no clinical or hematologic changes resulted, the tissues of 2 of these patients showed evidences of the effect of early irradiation. Two others showed no change, and the fifth showed almost complete destruction of leukemic foci in the bone marrow.

In the second group, 4 patients treated for longer periods showed definite improvement both clinically and hematologically. Pathologically there was also evidence of the effect of irradiation in 2 cases.

In the third group of 3 patients treated for several months, true remissions occurred both clinically and hematologically. However, in 2 patients a relapse with fatal termination followed within a short time. The third patient is still under treatment. Tissues from these patients showed pronounced effects of irradiation.

Spontaneous remissions have been seen in about 10 per cent of the 200 cases previously followed by us. However, the higher incidence of remissions and the

changes seen in the tissues of the patients reported in this study are encouraging results. Further trial and study of the effects of radioactive phosphorus in the treatment of children with leukemia seems justified.

The Influence of Maturity Upon the Growth of Certain Neurotropic Viruses in Vitro. Dr. F. Howell Wright, New York.

Excised brain tissue from mice of various ages was tested for its ability to supply the cellular factor required by the virus of St. Louis encephalitis and the virus of eastern equine encephalomyelitis for in vitro growth. Fetal or newborn mouse brain supports growth for months; 6 to 10 week old brain supports virus activity transiently or not at all. Over this same age gradient mice also lose their susceptibility to peripheral injection of these same viruses, but it cannot be assumed that studies on excised brain tissue necessarily explain phenomena occurring in the intact animal. The technic offers a method of studying the requirements for growth of neurotropic viruses.

The Isolation of Virus from a Patient with Fatal Encephalitis Complicating Measles. Dr. M. F. Shaffer and Dr. G. Rake, New Brunswick, N. J., and Dr. H. L. Hodes, Baltimore.

This paper will be published in full in a later issue of the American Journal of Diseases of Children.

An Agglutinogenic Intradermal Test for Susceptibility to Whooping Cough. Earl W. Flosdorf, Ph.D., Philadelphia; Dr. Harriet M. Felton, Philadelphia; Dr. A. Bondi, Rochester, N. Y., and Dr. Aims C. McGuinness, Philadelphia.

The material used for this intradermal test is obtained from Haemophilus pertussis organisms maintained in phase 1 by the cryochem process. The whole organisms are treated by sonic vibration, and the resulting extract is purified in such a way that only the so-called agglutinogen remains.

Since this material represents a fraction of the organism, we feel that the results obtained in the intradermal test are more consistent than results obtained by using whole organisms or the more complex substances which have been used unsuccessfully up to this time.

Over 200 children have been tested, with no untoward reactions. Known groups of children who have been vaccinated against pertussis and children with a history of the disease give positive reactions. Children between 6 and 14 months of age with no history of the disease or immunization give negative reactions. The reactions have been checked in most cases by agglutination tests using phase 1 Haemophilus pertussis as the antigen.

At present, an epidemic in an institution is being studied, and the results of the intradermal tests obtained have corresponded closely with the results from the groups of children known to have the disease.

Book Reviews

Solving School Health Problems. By Dorothy B. Nyswander, Ph.D. Price, $2.00. Pp. 363, with no illustrations. New York: The Commonwealth Fund, 1942.

Here is a more penetrating analysis of what a school health program might mean than any previous publication that this reviewer has read. It establishes new social frontiers, and yet its philosophy does not conflict with either extreme of the current controversy concerning medical practice. It should meet the approval of the most rugged defenders of private practice on the one hand and on the other appeal to the advocates of more socialization of medicine. It contributes to social medicine without avoiding issues, and it certainly presents no straddling compromise. It is based on a pragmatic concept of what American medicine and education might do for children and avoids the error of attempting too much. It relies more on education than on a paternalistic government to provide medical service. But education is not emphasized as an excuse for neglect of the needs of those who cannot or do not care for themselves. Rather, school and health authorities are seen as part of the community scheme for medical care—offering education and individual guidance in the use of medical facilities. For the community they offer sound evidence concerning how much and what kind of medical service is needed.

This approach to school health problems offers a new contribution to the distribution of medical care. It proposes an objective for public administration that every American practitioner should approve, i. e. "not to do things *to* and *for* people but to teach them to do things for themselves." This ideal should bring medicine and education together in a common cause. Surely, every practitioner should recognize that public education ought to create more demand for medical health supervision rather than mere examinations. If the future of pediatrics is to offer any possibilities for preventive service for the school age child, there must be more effective education of parents and children to use medical service intelligently.

This philosophy works out so consistently with the platform of the American Medical Association that the author might very well have proposed the Association's principle "the utmost utilization of qualified medical and hospital facilities already established." Education of parents to use the medical and hospital facilities already established is, of course, essential in any scheme for medical care, and yet how often public health effort gets bogged down in attempts to develop new services rather than to utilize what is already established.

The author and her co-workers recommended a new service in only one instance, and then in accordance with the principle that definite evidence of need was established. The evidence showed many confused and doubtful reports of cardiac disease or supposed cardiac disease among school children and too many children with rheumatic fever who did not get the protection needed. They proposed a cardiac consultation service to be used both by private physicians and physicians in the schools.

The policies proposed are a challenge to the medical profession because of their consistency with the principles of organized medicine. Short cuts to make medical service available through questionable or untried channels find no place here. Rather, a slower and less spectacular policy is adhered to, because the underlying philosophy is concerned with education as a means of social progress.

Of course it is one thing to start with sound objectives and a well thought out philosophy, but the administration of a service must apply policies, procedures and health bookkeeping so that practice really matches theory. The method of

Dr. Nyswander is a step by step analysis of needs and experimentation before widespread application. She tried out and reports various ways of making medical advice more readily accessible and more soundly conceived. She describes the ways the staff brought about more feeling of responsibility on the part of parents and how they cut down the chances of neglect. She makes clear how practices may be checked in order to carry out the objectives. As the experience in a few schools has shown that organized effort can improve the service, the citywide program of New York has been changed.

The material is well organized and contains so many illustrations of problem solving that school medicine is seen as a challenging branch of medicine that should intrigue the interest of any forward looking pediatrician.

Medical Genetics. By Laurence H. Snyder, Sc.D. Price, $1.50. Pp. 122, with 24 illustrations and diagrams. Durham, N. C.: Duke University Press, 1941.

Dr. Snyder has held for some ten years a unique position as professor of medical genetics at Ohio State University and is widely known as the author of one of the most readable books on the principles of genetics. This little book on the application of genetics to medicine is based on his lectures to his students at Columbus and on a series delivered in 1941 to the student body of the medical schools of Duke University, Wake Forest College and the University of North Carolina under the auspices of the Carnegie Corporation.

Experimental genetics has made great strides in the last quarter-century. The fundamental principles of heredity are well worked out and are constantly receiving important day to day application in the breeding and development of lower animals and plants. The application of these principles to human genetics has necessarily lagged, because of the impossibility of using experimental methods in this field and the need of developing special technics. Much has, however, been accomplished, both as to the heredity of normal human traits and as to the mechanism of disease inheritance. This study of the heredity of disease has an important clinical bearing, not only because it leads to a better understanding of many diseases but because it often gives definite help in diagnosis and may aid the physician to give his patient valuable advice as to the management of his life in view of a handicap of hereditary transmissible disabilities.

The average physician is not likely to have the knowledge of genetic technic requisite for the untangling of complicated genetic problems. He is the one, however, who must collect the facts for the geneticist's analysis, and such collection, to be useful, demands some understanding of how the geneticist works. The aim of Dr. Snyder's lectures is to present briefly and simply the known facts of the heredity of disease and the types of hereditary transmission involved and, largely by inference, to indicate what physicians might be doing to aid the geneticists in their study of these problems. There is no difficult technical discussion like that which one meets in such a treatise as Snyder's larger book, and unfamiliar terms are explained as they come up in the course of the text. The titles of the lectures indicate the book's scope. They are: (1) The Study of Human Heredity (general remarks on the applicability of genetics to clinical problems); (2) Medico-Legal Applications (chiefly regarding blood types); (3) Mental Disorders; (4) Eye and Ear Abnormalities; (5) Abnormalities of the Skin; (6) Skeletal and Muscular Abnormalities; (7) Diatheses and Susceptibilities (presenting present knowledge regarding hereditary factors in such conditions as diabetes mellitus and thyroid disease); (8) Diseases of the Blood; (9) Cancer (an informative brief discussion of facts and theories on this important topic); (10) The Future Development of Medical Genetics (this chapter, which discusses methods by which further advances are to be hoped for, is the only one to introduce what might be termed difficult reading, which could hardly be avoided, as some of these methods are complicated and not readily understood by one without knowledge of the principles of genetics).

The book is well composed, readable and adequately illustrated. Dr. Snyder's reputation insures the accuracy of his statements. Every clinician might learn

something of value from a perusal of the book and might well be inspired to enlarge by keener observation the store of facts from which the geneticist derives his material.

A Manual of Endocrine Therapy. By Bernard L. Cinberg. Price, $3.25. Pp 178, with no illustrations. Brooklyn: Chemical Publishing Co., 1942.

In his introduction the author says, "It is a manual of endocrine therapy and includes only a minimum of theoretical discussion." It would therefore be unfair for a reviewer to criticize the book on these grounds.

As a guide to diagnosis and therapy the sections on the use of endocrine preparations in gynecology might be helpful to the busy general practitioner. In a sketchy way the therapeutic approach to most of the problems involving menstruation, pregnancy and sterility is indicated, but in no case is there sufficient detail to warrant use of the manual as the sole guide.

Most of the other chapters are wholly inadequate. Seven pages are devoted to an extraordinarily elementary discussion of the all-important subject of thyroid. A comparison of the amount of information contained in the same number of words on this subject in a standard textbook of pediatrics makes one wonder how so little could have been selected for this manual from the available material. The five pages devoted to worthless preparations of thymus, pineal, prostate and mammary glands might well have been omitted and the space utilized for more detailed information about thyroid.

To use the author's own words, "The large number of physicians in the United States who practice occasional endocrine therapy without a basic knowledge of the subject creates a problem which requires solution." In its present form it is doubtful whether this book goes far toward solving this problem.

Blood Grouping Technic. By Fritz Schiff, M.D., and William C. Boyd, Ph.D. Price, $5.00. Pp. 248 with 45 illustrations and 67 tables. New York: Interscience Publishers, Inc., 1942.

Of the three parts of this book, the first deals with the theoretic foundations of blood grouping. The second part treats the general technic of blood group investigation: apparatus; isohemagglutination; determination of blood groups with immune serums; the M and N types; subgroups of A and B, and the investigation of other materials than erythrocytes. The final part consists of special applications of technics of blood grouping, including blood transfusions, transfusion accidents, blood banks, preservation of blood, problems of relationship, forensic applications of blood grouping, related factors in animals and investigations of blood groups in anthropology.

This is a complete and excellent monograph. It aids the beginner by explaining the principles underlying the procedures, the technician by outlining all the various methods of blood grouping and the clinician by discussions of the use of preserved blood, blood substitutes, transfusion accidents and the donor problem. It is a beautiful piece of work and should be on the table of every one interested in any way in the subject of blood groups.

War Gases. By Morris B. Jacobs, Ph.D. Price, $3.00. Pp. 180, with 8 illustrations and 26 tables. New York: Interscience Publishers, Inc., 1942.

This book is an excellent and rather complete account of the chemistry of the war gases. There is only a brief and incomplete chapter on the pathologic effects of these gases and practically nothing on treatment of gas casualties. On the other hand, the subjects of recognition of gases and decontamination are thoroughly discussed.

This is a good book for the army gas officer and for the chemist, but is of only limited value to the clinician.